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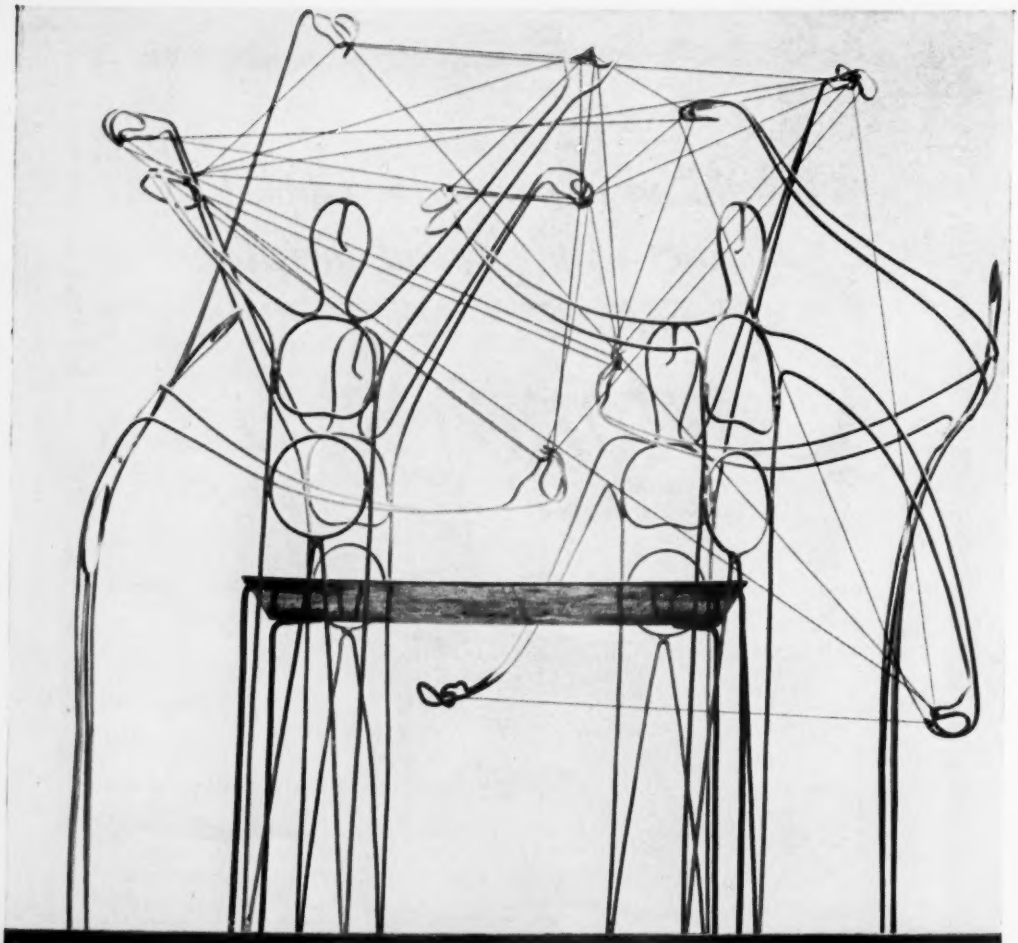

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USES AND MISUSES OF RADIOACTIVE IODINE IN TREATMENT OF CANCER OF THYROID

RULON W. RAWSON, M.D.

J. E. RALL, M.D.

AND

JACOB ROBBINS, M.D.

NEW YORK

THE EARLY studies with radioactive iodine by Hertz, Roberts, and Evans [1] and by Hamilton and Soley,[2] in which it was demonstrated that the natural avidity of the thyroid for iodine could be used to selectively deposit radioactive isotopes of iodine in thyroid tissues, led to the hopeful hypothesis that diseased thyroid tissue might be effectively irradiated by administering radioactive iodine to patients suffering with such maladies. Already it has been amply demonstrated in many clinics that exophthalmic goiter (Graves's disease) can be successfully treated with radioactive iodine. Indeed, the complete replacement of surgical and other forms of treatment by radioiodine is delayed only by an uncertainty as to its possible subsequent undesirable effects on the remaining thyroid tissue.

In following the above hopeful hypothesis, a group of investigators at Presbyterian Hospital and Columbia University reported the first attempts to localize radioactive iodine in cancers of the thyroid in 1942 [3] and 1944.[4] Their results were rather discouraging. However, in 1944 Leiter, Seidlin, Marinelli, and Baumann [5] reported studies on a previously thyroidectomized patient in whom hyperthyroidism developed, which resulted from an overfunction of extensive metastatic cancer of the thyroid. In 1946 the same investigators [6] reported on the successful treatment of their patient's metastatic cancer of the thyroid with radioactive iodine. Although such patients present a most dramatic picture, they are extremely uncommon. Indeed,

Read before the Section on Internal Medicine at the 102nd Annual Session of the American Medical Association, New York, June 2, 1953.

1. Hertz, S.; Roberts, A. and Evans, R. D.: Radioactive Iodine as an Indicator in the Study of Thyroid Physiology, Proc. Soc. Exper. Biol. & Med. **38**:510, 1938.

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3. Keston, A. S.; Ball, R. P.; Frantz, V. K. and Palmer, W. W.: Storage of Radioactive Iodine in a Metastasis from Thyroid Carcinoma, Science **95**:362, 1942.

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5. Leiter, L.; Seidlin, S. M.; Marinelli, L. D., and Baumann, E. J.: The Effect of Thiouracil on Hyperthyroidism and on Uptake of Radioiodine with Adenocarcinoma of Thyroid and Functioning Metastases, J. Clin. Invest. **23**:941, 1944.

6. Seidlin, S. M.; Marinelli, L. D., and Oshry, E.: Radioactive Iodine Therapy: Effect on Functioning metastases of Adenocarcinoma of the Thyroid, J. A. M. A. **132**:838, 1946.

we have seen only three such patients during the past five years. One of our patients is of unusual interest because of the dramatic effect produced on her tumor by the administration of only one large dose of I^{131}. Her case history follows.

A. G., a 59-year-old woman, was first seen at Memorial Center in November, 1950, complaining of having had massive hemoptysis three times during the two months prior to her admission. She had had a nontoxic goiter removed in 1926 and another in 1945 (on review, sections of the goiter removed in 1945 were diagnosed as alveolar and follicular carcinoma of the thyroid). The goiter had returned in 1949. A firm 6 by 6 cm. nodule was found in the midline of the neck, which was fixed to the skin and the underlying tissue. The skin was warm and moist and there was a fine tremor of the extended fingers. The pulse rate was 88 per minute. The basal metabolic rate was +24%, and the serum protein-bound iodine was 14.5 γ per 100 cc. X-ray examination of the chest revealed diffuse minimal nodular densities consistent with the picture of pulmonary metastases from cancer of the thyroid.

A tracer dose of radioiodine was given; in 48 hours 26.7% was excreted, 13% was concentrated in the neck, and there was a high degree of radioactivity over the chest, i. e., up to 15.9 counts per minute per administered microcurie at skin contact (background measurements were 0.1 count per minute per microcurie). On Jan. 4, 1951, the patient received 254 mc. of I^{131}. Of this dose 31% was excreted in 48 hours. Within six weeks after the radioiodine was administered the chest x-ray showed considerable decrease in the amount of tumor tissue. Now the chest x-ray is almost normal.

Notwithstanding these dramatic effects which have been observed in a few cases, such avidity for radioiodine by most cancers of the thyroid is not demonstrable. Indeed, the studies by Fitzgerald and Foote [7] on 100 cancers of the thyroid demonstrated that only 46% of these tumors concentrated measurable amounts of I^{131} and that those cancers which did concentrate radioiodine usually presented some colloid-bearing follicles in their structures. These authors also observed that even those tumors with respectable follicular structures usually concentrate in a patchy fashion considerably less radioiodine than does normal thyroid tissue.

Before discussing the constructive uses of I^{131} in the treatment of cancer of the thyroid, we wish to present some of what we now call misuses of radioiodine. Examples of these misuses for the most part are taken from some of our own early experiences. One will be the case of a patient that we have seen more recently, after his treatment elsewhere.

Some of our earlier attempts to treat metastatic cancer of the thyroid with radioactive iodine were without therapeutic effect. This was true probably because we were satisfied with minimal, even poor, uptake of the isotope by the metastatic lesions. In at least one instance, treatment with several large doses of I^{131}, most of which was excreted, probably hastened the patient's death. This patient's history follows.

P. G., a 38-year-old woman, was admitted to Memorial Center on March 17, 1947. She had had an "adenoma" (which on review proved to be an alveolar adenocarcinoma of the thyroid) removed in 1940. She had been well until December, 1946, when pain in the right lower jaw developed. A mass appeared in the right subparotid area shortly afterward and rapidly increased in size. A biopsy of the mass on admission revealed metastatic alveolar adenocarcinoma of the thyroid. Further studies revealed additional metastases in the lungs, right femur, lumbar spine, and sacrum. Preliminary tracer studies indicated measurable but completely inadequate collections of radioactive iodine by the mandibular and femoral metastases. The remaining, normal

7. Fitzgerald, P., and Foote, F. W.: The Function of Various Types of Thyroid Carcinoma as Revealed by the Radioautographic Demonstration of Radioactive Iodine, J. Clin. Endocrinol. **9**:1153, 1949.

thyroid tissue was ablated by administering 61 mc. of I^{131} on April 10, 1947. This was followed by a minimal increase in the percent of radioiodine concentrated by the metastases. However, urinary excretion of the test and therapeutic doses remained greater than 80%.

Because the metastases were growing very rapidly, we very naively resorted to heroic measures and administered radioiodine in doses of 61 mc. on April 10, 1947; 10 mc. on June 16, 1947; 93 mc. on Nov. 6, 1947; 184 mc. on Dec. 31, 1947, and 250 mc. on May 29, 1948. This program was associated with continued falls in hemoglobin level and white cell counts. Finally, a pancytopenia developed, and the patient died. At autopsy we failed to demonstrate any radiation changes in any of the various metastatic lesions.

Unfortunately, we are seeing patients who have been treated empirically with frequent comparatively small doses of radioactive iodine by the calendar rather than by considerations of the capacity of such tumors to concentrate radioiodine or of the radiosensitivity of the tumors. It is even more unfortunate to find that some of these patients have disease localized to the neck, which could be removed by competent surgeons.

The following case history is that of a retired Army Colonel, who was seen by one of us in consultation with Dr. Hollon W. Farr, and it illustrates these misuses of radioiodine.

P. H., aged 62, was first seen on Dec. 29, 1952. He gave a history of having had a left hemithyroidectomy in 1921 for what was called a "benign aberrant thyroid." In July 1949 he had been admitted to a hospital in another community because of growing masses in his neck. Biopsy had been done on these, and a diagnosis of metastatic adenocarcinoma of the thyroid to cervical lymph nodes had been made. A series of treatments with I^{131} was then started, consisting of 35 mc. per month, without prior tracer studies or determination of urinary excretion of the therapeutic doses administered. The patient stated that he had been told that it would require a total of 1,000 mc. to effect a cure. At the time that we saw him, he had already received 650 mc. Because the nodes were continuing to enlarge, the patient felt that he should seek other opinions. Because of the obstructive nature of his disease and because we found the disease localized to the neck and the superior mediastinum, we advised adequate surgery, which was performed in one of the service-connected hospitals.

As nearly as we could learn, there was no accurate information as to the amount of radioiodine retained in the tumors of this patient. Indeed, measurements that we made on this patient within 10 days after his last treatment revealed that practically no radioiodine was then present in the body. The fact that the disease was successfully removed surgically highlights another serious misuse of radioiodine.

The administration of frequent relatively small (35 mc.) doses of radioiodine we believe to be another misuse, since such doses are rarely large enough to exert any therapeutic effect but frequently seriously hamper subsequent treatment with this agent. Indeed, it has been our experience that even maximum function in a metastatic carcinoma of the thyroid, induced by methods to be discussed later, often is abolished by administering small therapeutic doses of radioactive iodine. This is illustrated by the following case report.

F. M., a 13-year-old girl, was first seen at Memorial Hospital in April, 1948, because of a known papillary and follicular adenocarcinoma of the thyroid with nonfunctioning pulmonary and cervical node metastases. Six months after the administration of a "thyroidectomizing" dose of I^{131} 60.6% of a tracer dose of I^{131} was excreted and measurable amounts of radioactive iodine were being concentrated in the metastases. Six months later 59.3% of a tracer dose was excreted and radioiodine was being concentrated in the metastatic lesions to the same degree. Treatment with thiouracil was then started, 1.0 gm. daily. Within three months only 28% of the dose was being excreted. This degree of function continued without further improvement for another five months. It was then planned to administer several 25-μc doses of I^{131}. Of the first therapeutic dose, 38% was excreted. Unfortunately, after this first therapeutic dose,

which exerted no objective beneficial effects on either the cervical or the pulmonary metastases, the functional capacity of the tumor decreased. Within three weeks after the first therapeutic dose was administered 75% of a test dose was being excreted. Notwithstanding the good effect induced by thiouracil prior to the first therapeutic dose, continued treatment with thiouracil for one year decreased the urinary excretion of radioiodine very slowly from 73% to 47% (Fig. 1).

We have also observed that x-radiation may similarly abolish the ability of these tumors to concentrate radioactive iodine.

Having been actively engaged in this study for nearly 10 years, we have formulated the following philosophy and methodology as to the use of radioactive iodine in treating cancer of the thyroid. We accept for possible treatment with radioactive iodine only those patients with cancer of the thyroid whose disease cannot be removed by a competent and experienced surgeon. We do not administer radioactive

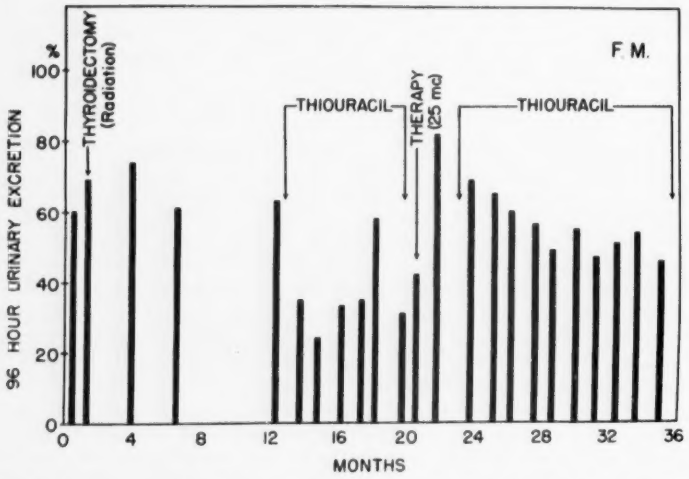

Fig. 1.—Urinary excretion of I^{131} (96 hours) in patient F. M. It is to be noted that after original treatment with thiouracil the patient excreted a small per cent of the radioiodine; after a therapeutic dose (25 mc. I^{131}) smaller fractions of the tracer doses of iodine were retained for over a year.

iodine to such patients unless their tumors have a natural or an induced avidity for radioactive iodine great enough to permit the safe administration of doses of radioactive iodine that might be expected to have a therapeutic effect.

As was indicated above, those patients whose tumors have an adequate natural avidity for radioiodine are very uncommon. We have, however, been able to induce a maximal function in a fair percentage of our patients.

During the past six years at Memorial Center we have accepted for study and possible treatment with radioiodine 52 patients with metastatic cancer of the thyroid whose metastases had minimal or no function. These patients were subjected to total thyroidectomy either surgically or with radioactive iodine. In 26 of these patients we have observed one or more metastases to develop a significant capacity to concentrate radioactive iodine within six months. This is demonstrated by the following case history.

I. M., a 54-year-old Negro woman, was admitted to the James Ewing Hospital on Sept. 16, 1952. She had been well until 1947, when a partial thyroidectomy was done for a moderate-sized goiter. The diagnosis was "fetal adenoma." In 1949 the goiter recurred. In November, 1951, the patient noted right lower back pain with radiation to the right knee. This increased and became incapacitating.

She was then admitted to New York Hospital, on July 25, 1952, where she was found to have a bulky thyroid tumor in both sides of the neck anteriorly. There was tenderness over the third lumbar vertebra, pain on raising the right leg, decreased ankle and knee reflexes on the right, and some sensory changes in the left thigh. Serum calcium, phosphorus, and alkaline phosphatase levels were normal. The basal metabolic rate was + 3%. X-rays revealed the trachea displaced to the left; there were multiple small nodules in both lung fields and osteolytic metastases in the skull, pelvis, left femur, and spine, with collapse of the third lumbar vertebral body.

A tracer dose of I^{131} on Aug. 2, revealed 13.4% uptake in the neck and 56.1% in the urine. Minimal uptake was demonstrated in the metastases. Total thyroidectomy with excision of the neck nodes was done on Aug. 7. The diagnosis was follicular and alveolar carcinoma of the

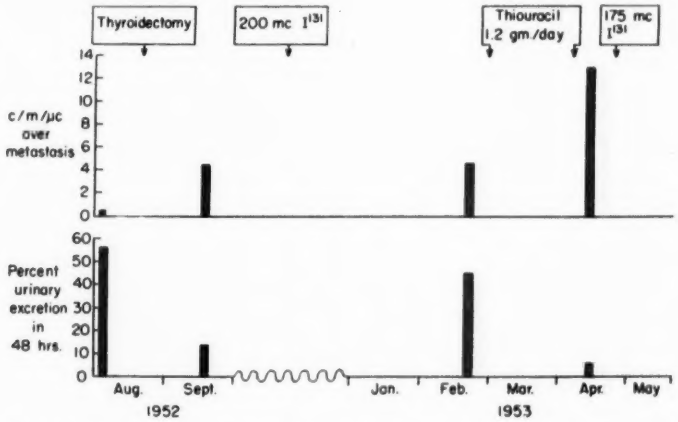

Fig. 2.—Urinary excretion of patient I. M. and radioactivity over metastases determined by counting. It is to be noted that after thyroidectomy there was a marked decrease in urinary excretion and a significant increase in counts per minute per microcurie administered over the metastases. The same effects were later observed again after the administration of thiouracil.

thyroid. Thereafter, because of severe pain, x-ray treatment (about 2,000 r to four portals) was given to the lumbar spine. There was some relief of pain.

A tracer study on Sept. 8, revealed a neck uptake of 1.5% at 48 hours, 13.6% in the urine, and high in vivo uptakes in tumor areas in the skull, lungs, and femur (Fig. 2).

The patient was transferred to the research ward of the James Ewing Hospital on Sept. 16, where after tracer studies of blood levels she received a 200 mc. dose of I^{131} on Oct. 3, 1952.

This marked change in function cannot be accounted for by the simple removal of a competitive tissue. We attribute this interesting biological characteristic of certain cancers of the thyroid to the fact that these tumors are capable of responding to the organism's need and assuming the functions of the normal parent organ. We suspect, but we have been unable to prove, that this occurs as the result of an increased secretion and availability of thyrotrophic hormone. Indeed, in 5 out of 15 patients treated with thyrotrophic hormone we have been able to increase or induce significant function in one or more metastatic lesions.

We have observed the most significant changes in a group of 42 patients in whom the effect of total thyroidectomy had been followed for varying lengths of time. These patients were then given thiouracil in doses of 1.0 to 1.5 gm. daily for several months. In 25 of these patients a marked to maximum function has developed within 30 days to three years. We attribute this phenomenon to the fact that thiouracil not only induces hypothyroidism but also augments the action of thyrotrophic hormone.

We are fully aware that from the patients' point of view it would be more desirable if we were able to keep them in a euthyroid state. However, we believe that in treating a disease such as metastatic cancer of the thyroid every effort be made to eradicate the disease. We believe that the results illustrated in the following history justify this extreme procedure.

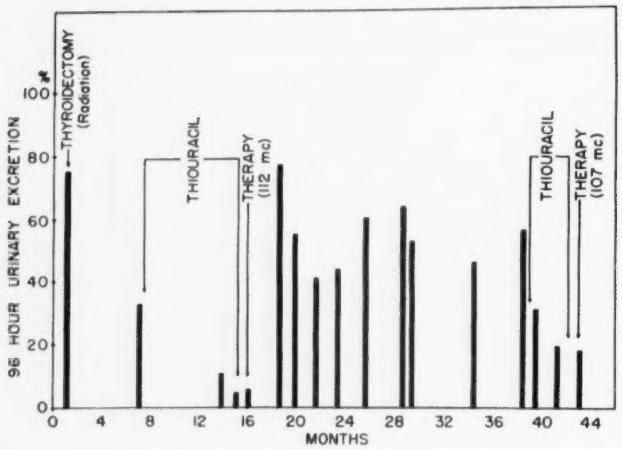

Fig. 3.—Urinary excretion of I^{131} (96 hours) by W. M. It is to be noted that after thyroidectomy there was a significant decrease in the excretion of radioiodine. This was maximally effected after treatment with thiouracil. After a therapeutic dose, there was an increased urinary excretion lasting nearly 18 months, following which thiouracil again exerted a maximum effect.

W. M., a 15-year-old white boy, was admitted to Memorial Hospital in May, 1947. He was found to have a low-grade follicular adenocarcinoma of the thyroid with diffuse pulmonary metastases, which on x-ray examination appeared as miliary nodular densities throughout both lung fields. He was also found to have rheumatic heart disease, with a Grade 4 mitral stenosis. A preliminary tracer study revealed no measurable uptake of radioiodine in the pulmonary metastases. In September 1947 a thyroidectomizing dose of I^{131} (25 mc.) was administered. After a test dose in April 1948 significant amounts of I^{131} were found to be concentrating in the pulmonary lesions. At that time, prolonged treatment with thiouracil, up to 1.5 gm. daily, was undertaken. This program was continued until December, 1948, when on two occasions the excretion in the urine of a tracer dose of I^{131}, given 48 hours after discontinuing administration of thiouracil, was 5% or less. On Dec. 29, 1948, a therapeutic dose of 112 μc was administered. Only 6% of this dose was excreted during the first 96 hours, and the blood level did not rise above 0.67 % of the dose per liter of blood. As a result of this irradiation, there occurred a 70% decrease in total lymphocytes but no significant decrease in total white cell count. Serial roentgenograms of the chest showed a progressive decrease in tumor mass, which was maximum

by July, 1950. Notwithstanding this striking improvement, the patient still had disease, which, after a maximum avidity for I^{131} had been acquired, was treated subsequently with two large doses of I^{131} (Figs. 3, 4, and 5).

In our clinic those patients with metastatic carcinoma of the thyroid who are under consideration for treatment with radioiodine are first evaluated as to the capacity of their tumors to concentrate radioiodine by administration of tracer doses of the isotope. The urine is collected usually for 96 hours, and at the end of 48 hours in vivo measurements are made over the neck area and over demonstrable metastatic

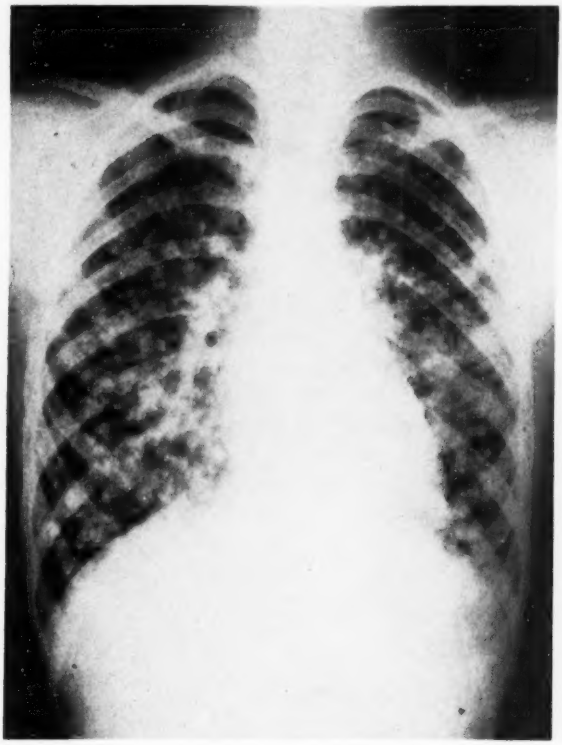

Fig. 4.—Chest x-ray of W. M. prior to therapy, taken Dec. 28, 1948.

lesions. Over the metastatic lesions we are usually unable to quantitate the per cent of the administered dose concentrated by such cancerous tissue. However, for subsequent comparisons we record the counts per minute at skin contact divided by the number of microcuries administered. After ablation of the normal thyroid, tracer studies are done every four to six weeks for three to six months. At that time, thiouracil in doses of 1.0 to 1.5 gm. daily is administered. Each six to eight weeks administration of the drug is stopped and another tracer test is made 48 hours later. With this test, the urinary activity is followed for 96 hours and in vivo measurements are made over the known tumors. If the urinary excretion is less than 40% of the administered dose, we consider the patient a candidate for treatment and a

second, but larger, test dose of I^{131} is given, after which daily urinary excretion is determined, in vivo measurements are made over the tumor at 48 hours, and the blood level is determined daily for at least seven days and plotted graphically.[8] From the graphic plot of blood levels and the I^{131} retained in the body we calculate the amount of radiation that will be delivered to the hemopoietic system and other extrathyroidal tissues. Generally, we attempt to deliver to the blood, on the basis of

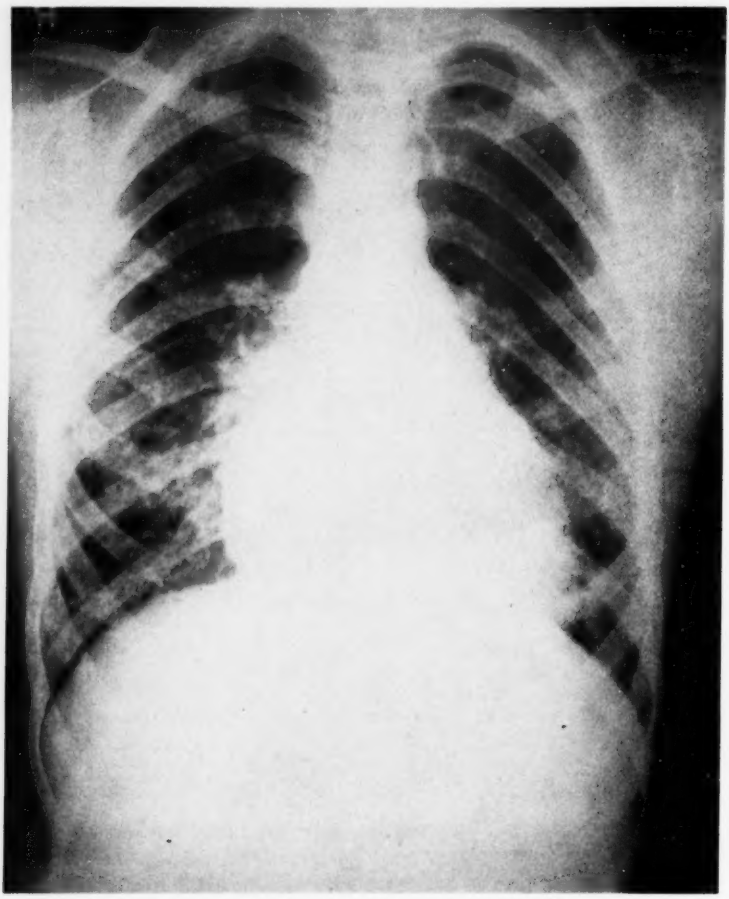

Fig. 5.—Chest x-ray of W. M., taken July 1, 1950.

the integrated amount of radioiodine in the blood (using a factor of 10.2 rep per gram per day), less than 400 rep. From the above calculation and the estimated size of the tumor we try to determine whether we can deliver a cancerocidal dose of I^{131} without doing the patient serious harm. We then administer a maximum but safe

8. Rall, J. E.; Foster, C. G.; Robbins, J.; Lazerson, R.; Farr, L. E., and Rawson, R. W.: Dosimetric Considerations in Determining Hematopoietic Damage from Radioactive Iodine, Tr. Am. Goiter A. p. 209, 1952.

dose of radioactive iodine. After the therapeutic dose, we make the same determinations of urinary activity, activity over the tumors, and the radioactivity in the blood. The peripheral blood is followed closely for changes in hemoglobin, total white cell count, and total lymphocytes, and the platelets for at least three weeks after administration of the dose of I^{131}.

By following these rather rigid criteria in treating cancer of the thyroid, we have demonstrated that (1) a large percentage of cancers of the thyroid can be made to assume certain functions of normal thyroid tissue, and (2) certain cancers of the thyroid can be at least partially destroyed with radioactive iodine. Our therapeutic results are as follows:

Number of patients treated	35
Number with sustained objective improvement	10
Number showing transient objective improvement	10
Number of treatment failures	8
Number treated too recently for evaluation	7

Notwithstanding the fact that in at least one of our patients no disease is now demonstrable, we are unwilling to speak of cures. Indeed, we consider it a folly to speak of cures of this disease in patients followed less than 20 years. We would list, then, as another misuse of I^{131} in treating cancer of the thyroid the discussion of cure.

SUMMARY

Radioiodine should be used for treating cancer of the thyroid (1) in those patients whose disease cannot be removed by a competent surgeon; (2) in those patients whose cancers are capable of concentrating cancerocidal doses of radioiodine without serious damage to extrathyroidal tissues.

The misuses of radioiodine in the treatment of cancer of the thyroid occur (1) when it is used for patients whose disease could be removed by a competent surgeon; (2) when it is used for patients whose tumors concentrate so little of the isotope that a therapeutic effect is impossible; (3) when so little I^{131} is used that it destroys only the function without any therapeutic effect; (4) when the I^{131} is administered in doses which are so great (single or cumulative) that serious body radiation occurs.

TOXOPLASMOSIS

III. Study of Families Exposed to Their Toxoplasma-Infected Pet Dogs

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THERE are many potential sources of Toxoplasma infection in nature, but it is not known which is most important for man. The disease occurs in many species of animals and birds, including the rabbit, gondi, dog, mole, pigeon, mouse, rat, squirrel, monkey, guinea pig, wombat, baboon, vole, canary, chimpanzee, sheep, cat, and chinchilla. Twenty-seven fatal cases of toxoplasmosis (13 mammals and 14 birds) over a 10-year period were reported from the Philadelphia zoo.[1] Recently, we reported the isolation of Toxoplasma from swine, thus extending the host range to a new species.[2]

The organism, Toxoplasma gondii, causing animal infection, is morphologically, antigenically, and pathogenically similar to the organism causing the disease in man. Various animal reservoirs have been suggested as potential sources of human infections.[3] More evidence is needed to substantiate the belief that animals serve as the

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This investigation was supported in part by a research grant from the National Institutes of Health, Public Health Service.

Dr. Leon Jacobs performed two human and three animal dye tests, and Dr. Claude S. Perry examined two of the patients.

1. Ratcliffe, H. L., and Worth, C. B.: Toxoplasmosis of Captive Wild Birds and Mammals, Am. J. Path. **27**:655-667, 1951.

2. Farrell, R. L.; Docton, F. L.; Chamberlain, D. M., and Cole, C. R.: Toxoplasmosis: I. Toxoplasma Isolated from Swine, Am. J. Vet. Res. **13**:181-185, 1952.

3. Feldman, H. A., and Sabin, A. B.: Skin Reactions to Toxoplasmic Antigen in People of Different Ages Without Known History of Infection, Pediatrics **4**:798-804, 1949. Eyles, D. E.: Toxoplasma in the Norway Rat, J. Parasitol. **38**:226-229, 1952. Cowen, D., and Wolf, A.: Toxoplasmosis in the Monkey: Acute Fatal Infection Experimentally Produced in Young Macaca Mulatta, J. Infect. Dis. **77**:144-157, 1945. Manwell, R. D., and Drobek, H. P.: Mammalian Toxoplasmosis in Birds, Exper. Parasitol. **1**:83-93, 1951. Grocott, R. G.: A Case of Canine Toxoplasmosis from the Canal Zone, Am. J. Trop. Med. **30**:669-675, 1950. Frenkel, J. K., and Friedlander, S.: Toxoplasmosis, Public Health Bulletin No. 141, Federal Security Agency, U. S. Public Health Service, 1951. Otten, E.; Westphal, A., and Kajahn, E.: Zur Epidemiologie der Toxoplasmose: Der Hund als Infektionsquelle des Menschen, Klin. Wchnschr. **29**:343-346, 1951.

reservoir for human toxoplasmosis. If animals are important in the epidemiology of human toxoplasmosis, dogs should be good subjects for study, because they suffer from spontaneous infection and are intimately associated with human families. Therefore, a program was developed to study the human contacts of Toxoplasma-infected dogs. Conversely, whenever the diagnosis of toxoplasmosis was established for humans the animal contacts were studied for the presence of concurrent or previous infection. The purpose of this report is to describe the results of such a survey.

MATERIALS AND METHODS

Twenty-eight Toxoplasma-infected dogs admitted as patients to the Ohio State University Veterinary Clinic and 115 animals which died as the result of toxoplasmosis epizootics in two dog kennels were available for study. The presence of Toxoplasma infection was confirmed by the following laboratory methods: (1) animal transfer studies to isolate Toxoplasma gondii, using at least three white Swiss mice for each inoculum of organ emulsion or body fluid [4]; (2) serologic studies, using the cytoplasm-modifying method of Sabin and Feldman [5]; (3) histopathologic study of biopsy and autopsy tissues.

Whenever possible, human contacts of these infected dogs were examined for evidence of toxoplasmosis. Each person was given a physical examination, and a toxoplasmin skin test was done after blood was drawn for the cytoplasm-modifying serologic test. Attempts were made to isolate Toxoplasma from three human patients by animal inoculation of body fluids and tissues. As soon as a diagnosis of Toxoplasmosis was established in human patients, their pets were studied for evidence of the same infection.

RESULTS

The families who owned 12 of the 28 Toxoplasma-infected pet dogs presented themselves for examination at the Ohio State University Hospital. The results of serologic tests and toxoplasmin intradermal tests for each of the 37 persons examined are summarized in the Table. This table also presents evidence for the diagnosis of toxoplasmosis in each pet and shows which persons were exposed to each of the dogs.

A diagnosis of toxoplasmosis for all pet dogs included in the Table was confirmed by one or more of the methods described above. Of the 12 pets presented, Toxoplasma was isolated from the organs of 7 by mouse inoculation. Organisms were demonstrated in the tissues of all 12 by histological study of organs collected at autopsy. Sera from nine pets were tested for Toxoplasma antibodies, and all had a titer greater than 1:16. The titers ranged from 1:20 to 1:320. Toxoplasma organisms were demonstrated in all dogs possessing a serologic titer of 1:16 or over. In previous studies on experimentally infected dogs we found that a cytoplasm-modifying titer of 1:16 or greater was evidence of current or past toxoplasmosis.[6]

Thirty-five of the 37 persons who had been exposed to their infected pets proclaimed themselves to be in good health. Physical examination of these 35 persons

4. Chamberlain, D. M.; Docton, F. L., and Cole, C. R.: Toxoplasmosis: II. Intra-Uterine Infection in Dogs, Premature Birth and Presence of Organisms in Milk, Proc. Soc. Exper. Biol. & Med. **82**:198-200, 1953.

5. Sabin, A. B., and Feldman, H. A.: Dyes as Microchemical Indicators of a New Immunity Phenomenon Affecting a Protozoon Parasite (Toxoplasma), Science **108**:660-663, 1948.

6. Docton, F. L.; Cole, C. R., and Chamberlain, D. M.: Unpublished data.

failed to reveal evidence suggestive of active toxoplasmosis. Ten persons were sensitive to toxoplasmin, and Toxoplasma antibodies were demonstrated in the sera of nine. Cytoplasm-modifying titers greater than 1:16 were interpreted as indicative of current or past Toxoplasma infection.[7]

Human Household Contacts of Dogs with Toxoplasmosis

Families Exposed to Infected Dogs					Evidence of Toxoplasmosis in Pet Dog			
Patient No.	Age, Yr.	Sex	Skin Test, Mm.	Dye Test*	Dog No.	T. Isol.†	Dye Test*	Organs in Which T. Was Found‡
1	28	M	0	0	25	+	1:80	Lung, tonsil, bronchial node, heart
2	26	F	12 × 18	1:160				
3	30	M	0	0	24	..	1:64	Stomach, liver, mesenteric node, heart
4	28	F	15 × 30	1:256				
5	35	M	.....	0	278	+	1:64	Mesenteric and bronchial node
6	32	F	.....	1:256				
7	3	M	.....	1:1024	279	..	1:64	Lung, bronchial node, heart, parathyroid
8	27	M	0	0				
9	28	F	0	1:160	509	+	1:80	Cecum, mesenteric node
10	3	M	0	1:20				
11	1	F	0	.....				
12	37	M	.....	0	36	+	1:256	Intestine, cecal node, liver, kidney, spleen
13	31	F	.....	0	428	+	1:20	Lung, bronchial node, mesenteric node, intestine, spleen, brain
14	11	F	.....	0	538	..	....	Lung, heart
15	38	M	0	0				
16	37	F	10 × 18	1:10				
17	16	F	0	0				
18	14	M	0	0	526	+	1:320	Lung, intestine, bronchial node, spleen, pancreas
19	12	F	12 × 20	1:10				
20	17	F	12 × 20	1:20				
21	11	F	0	0	520	..	....	Lung
22	25	M	5 × 5	0				
23	25	F	12 × 18	0				
24	31	F	0	.....				
25	28	M	15 × 30	0				
26	26	F	14 × 30	0				
27	12	F	.....	0				
28	63	F	10 × 18	0				
29	4	M	0	0	86	+	1:40	Liver, spleen, heart, adrenal gland
30	10	F	0	0				
31	1	F	0	0				
32	44	M	.....	0	157	..	....	Tonsil, cecum, cervical node, prostate, brain
33	39	F	.....	0				
34	47	M	.....	0				
35	46	F	.....	0				
36	18	F	.....	0				
37	14	F	.....	0				

* Sabin-Feldman cytoplasm-modifying test.
† Recovery of Toxoplasma by mouse inoculation.
‡ Microscopic demonstration of Toxoplasma in tissue sections.

Titers of 1:10 in two patients (Patients 16 and 19) were considered insignificant, but titers of 1:20 to 1:1,024 in seven were interpreted as evidence of present or past Toxoplasma infection. Serum from a 26-year-old asymptomatic woman (Patient 2) contained Toxoplasma antibody through a dilution of 1:80, and one

7. Sabin, A. B.; Eichenwald, H.; Feldman, H. A., and Jacobs, L.: Present Status of Clinical Manifestations of Toxoplasmosis in Man: Indications and Provisions for Routine Serologic Diagnosis, J. A. M. A. **150**:1063-1069, 1952.

month later a titer of 1 : 160 was found. Toxoplasmosis developed in healthy white Swiss mice inoculated with blood, and Toxoplasma organisms were identified in peritoneal exudate obtained by paracentesis. With the same procedure, Toxoplasma organisms were isolated from the patient's blood a second time, six days later. Organisms were not found in her blood collected 30 days after the second isolation. Spontaneous infection in the mice was excluded by passage of lung, spleen, liver, and brain emulsions from the same stock. This case is described in detail in a separate report.[8] The patient's husband was insensitive to toxoplasmin, and his serum contained no Toxoplasma antibody.

Their pet dog (No. 25 in the Table) was fondled like a child in the household and was carefully nursed in the home during its illness. The pet was ill four weeks prior to admission to the Veterinary Clinic. A Toxoplasma antibody titer of 1 : 80 was found in the dog, and it reacted to toxoplasmin. Toxoplasma organisms were isolated by inoculation of mice with organ emulsions. Organisms were demonstrated histologically in the lung, tonsil, bronchial node, and heart. The presence of organisms in the tonsil and lung suggests that sputum and saliva might have contained Toxoplasma during the course of illness. When serum known to contain antibodies against canine Toxoplasma was used, the organism (newly isolated from the blood of Patient 2) manifested a definite cytoplasm-modifying phenomenon identical to that of the canine organism which had been used in the original titration of the serum. Inoculation of two dogs with Toxoplasma isolated from the blood of Patient 2 produced acute toxoplasmosis and stimulated the production of Toxoplasma antibody. The Toxoplasma of human origin was found to be morphologically, serologically, and pathogenically similar to the canine organism. This conforms to a previous observation in this laboratory, in which Toxoplasma organisms isolated from nine dogs were all found to be morphologically, serologically, and pathogenically similar to another human (RH) strain.

Patient 4, a 28-year-old white woman, entered University Hospital with encephalitis of six weeks' duration.[8] She reacted to toxoplasmin, and her serum contained Toxoplasma antibodies in a titer of 1 : 256, as measured by the dye test. The complement-fixation test was also strongly positive, suggesting recent infection. A clinical diagnosis of Toxoplasma encephalitis and neuroretinitis was made. This woman resided on a farm where she assisted her husband in the care of chickens, cattle, horses, dogs, and cats. A dog, 2 cats, and 12 chickens were subsequently brought to the College of Veterinary Medicine for study. No evidence of toxoplasmosis was found in studies of the cats and chickens. The dog (No. 24) was sensitive to toxoplasmin, and its serum contained Toxoplasma antibody in a titer of 1 : 64. Histological examination of organs collected at autopsy revealed Toxoplasma in lesions of the stomach, liver, mesenteric lymph node, and heart. Excretion of Toxoplasma in the feces or vomitus was possible, since organisms were seen in the walls of gastric ulcers.

A 3-year-old white boy (Patient 7), examined by Dr. Claude S. Perry, of the Department of Ophthalmology, was found to have chorioretinitis and manifestations

8. Prior, J. A.; Cole, C. R.; Docton, F. L.; Chamberlain, D. M., and Saslaw, S.: Toxoplasmosis: IV. Report of 3 Cases with Particular Reference to Asymptomatic Toxoplasma Parasitemia in a Young Woman, A. M. A. Arch. Int. Med. this issue, p. 314

of cerebral disease. The boy's serum revealed a dye test antibody titer of 1 : 1,024, and his mother's (Patient 6) serum had a titer of 1 : 256. The mother was asymptomatic and gave no history suggestive of Toxoplasma infection. Toxoplasmin and serologic tests in the father were negative. A diagnosis of toxoplasmic chorioretinitis and encephalitis (possibly congenital) was made for the boy. Antibody titers of 1 : 1,024 in the child and 1 : 256 in the mother are compatible with congenital toxoplasmosis in the boy. Nine dogs owned by the family were subsequently studied for evidence of toxoplasmosis. The sera from two dogs (No. 278 and 279) had titers of 1 : 64, and Toxoplasma organisms were demonstrated histologically in lesions of the mesenteric and bronchial lymph nodes of one dog (No. 278) and in the lung, bronchial lymph node, heart, and parathyroid gland of the second dog (No. 279). In addition, Toxoplasma organisms were isolated by animal inoculation from organ emulsions of the former dog. The distribution of Toxoplasma in the organs suggested potential dissemination of organisms in the sputum and feces.

The only positive findings in studies of the fourth family (Patients 8 to 11 in the Table) were a Toxoplasma antibody titer of 1 : 160 in the serum of the mother and a titer of 1 : 20 in the serum of her 3-year-old son. Both the mother and her son were asymptomatic. Their pet dog (No. 509) possessed an antibody titer of 1 : 80. Toxoplasma organisms were isolated by mouse inoculation from organs collected at autopsy, and histologically organisms were seen in the cecum and mesenteric lymph node.

Three asymptomatic female members of the seventh family (Patients 16, 19, and 20) were sensitive to toxoplasmin, and their sera contained Toxoplasma antibody. The serum titers of the mother (Patient 16) and of her youngest daughter were only 1 : 10; the serum titer of an unrelated girl in the same household was 1 : 20. One of their pet dogs (No. 526) had a Toxoplasma antibody titer of 1 : 320, and the organism was demonstrated in the lungs, intestine, bronchial node, spleen, and pancreas. Toxoplasma organisms were isolated from organ emulsions by mouse and dog inoculation. A second pet dog (No. 520) in the household died of toxoplasmosis. Mrs. C. M. (Patient 16) cared for not only these pets but also for 45 Chihuahuas, of which 14 pups and 15 adults died of toxoplasmosis.

Sera from members of three families (Patients 12 to 14 and 25 to 37) contained no demonstrable antibody. Two persons (Patients 13 and 14) not only were household contacts of two infected pets but also were caretakers of a kennel during the time of a toxoplasmosis epizootic among the dogs. In this kennel of 104 dachshunds toxoplasmosis was responsible for the death of 69 pups and 17 adults. Sera from the woman (Patient 13) and an unrelated girl assistant (Patient 14) contained no detectable antibodies, in spite of extensive exposure to infected dogs.

SUMMARY

The results reported here suggest that some relationship may exist between animal and human toxoplasmosis, although evidence of communicability is lacking. The following relationships may be more than coincidental: 1. Toxoplasma parasitemia was demonstrated in a 26-year-old woman who had cared for her Toxoplasma-infected pet dog during four weeks of its illness. 2. A pet dog owned by a 28-year-old woman with toxoplasmic neuroretinitis and encephalitis had active toxoplasmosis. 3. Two of nine dogs which were pets of a 3-year-old boy with Toxoplasma chorioretinitis and encephalitis had toxoplasmosis.

Toxoplasma organisms of human and canine origin were found to be morphologically, serologically, and pathogenically similar.

Demonstration of Toxoplasma in the lungs, tonsils, gastric ulcers, intestine, cecum, and kidneys suggests that sputum, saliva, vomitus, feces, and urine of infected dogs may be potential sources of infection.

Sera from 9 of the 37 persons having had household contact with their Toxoplasma-infected dogs possessed Toxoplasma antibodies. All except two of the nine sera containing demonstrable antibody came from young women; two were from young sons of mothers possessing high antibody titers. Five of the nine persons had significant antibody titers, ranging from 1:80 to 1:1,024. Of these five persons two had toxoplasmic chorioretinitis and encephalitis; Toxoplasma parasitemia was found in one; no abnormalities were detectable in two persons.

TOXOPLASMOSIS

IV. Report of Three Cases with Particular Reference to Asymptomatic Toxoplasma Parasitemia in a Young Woman

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HUMAN toxoplasmosis has been confined largely to congenital infection of infants. Acquired toxoplasmosis with clinical illness in the adult remains a rarity. On the basis of toxoplasmin skin reactivity and demonstrable circulating antibodies there is increasing evidence of widespread infection in man without clinical manifestations.

As a result of the development of a new serologic method of diagnosis,[1] long series of infants and children with congenital toxoplasmosis have been reported. Sabin and Feldman [2] reported 23 patients with congenital disease in 1948. Eichenwald [3] established the diagnosis for 100 patients from 1948 to 1952, and Feldman [3] found 75 patients from 1949 to 1952. Careful interrogation has uniformly failed to elicit any history of illness attributable to toxoplasmosis, either present or past, in the mothers of infants so affected. However, the mothers of infants with toxoplasmosis always show high Toxoplasma antibody titers, indicative of recent infection. Therefore, it is logical to assume that the mother must have had asymptomatic toxoplasmosis during her pregnancy to make possible this transplacental infection. The validity of this assumption can be substantiated only by the isolation of Toxoplasma from the blood of an apparently healthy human adult. Parasitemia has been demonstrated in experimental toxoplasmosis of mice, rats, rabbits, pigeons, and chicks by Jacobs and Jones.[4]

From the Departments of Medicine and Veterinary Pathology, Ohio State University.

This investigation was supported in part by a research grant from the National Institutes of Health, Public Health Service.

1. Sabin, A. B., and Feldman, H. A.: Dyes as Microchemical Indicators of a New Immunity Phenomenon Affecting a Protozoon Parasite (Toxoplasma), Science **108**:660, 1948.

2. Sabin, A. B., and Feldman, H. A.: Chorioretinopathy Associated with Other Evidence of Cerebral Damage in Childhood: Syndrome of Unknown Etiology Separable from Congenital Toxoplasmosis, J. Pediat. **35**:296, 1949.

3. Sabin, A. B.; Eichenwald, H.; Feldman, H. A., and Jacobs, L.: Present Status of Clinical Manifestations of Toxoplasmosis in Man, J. A. M. A. **150**:1063, 1952.

4. Jacobs, L., and Jones, F. E.: The Parasitemia in Experimental Toxoplasmosis, J. Infect. Dis. **87**:79, 1950.

In a study of human families exposed to their Toxoplasma-infected pet dogs we found one young woman with Toxoplasma parasitemia and another woman with toxoplasmic encephalitis and neuroretinitis.[5] It is the purpose of this report to present a detailed description of both women and their infected pet dogs. A fatal case of toxoplasmosis in a child in which the disease was "masked" by severe pertussis is also reported.

REPORT OF ANIMAL AND HUMAN CASES

CASE 1 (Dog owned by Mrs. J.).—A 3-year-old male cocker spaniel was presented on Jan. 10, 1952, to the Ohio State University veterinary clinic with an illness of four weeks' duration. The dog showed evidence of apathy, chilling, tenderness over the abdomen, and weakness of the posterior extremities.

Physical Examination.—The temperature was 103.4 F. Marked enlargement of the tonsils was seen, especially on the left. Respirations were rapid and shallow. A friction rub was heard in the left chest. Pressure over the kidneys elicited pain. There was incoordination of the posterior extremities.

Laboratory Data.—A blood cell count showed a hypochromic anemia and slight increase in white blood cells with persistent relative neutrophilia. A serologic test for leptospirosis was negative. The left tonsil was removed, and microscopic study revealed focal necrosis, hyperplasia of primary lymphoid follicles, and hemorrhage. Within and around the necrotic areas were numerous monocytes and reticuloendothelial cells, many of which contained from 3 to 25 deeply basophilic round to oval bodies measuring 1.5 by 2.0 μ. Some elongated and falciform forms morphologically were typical of Toxoplasma, and a diagnosis of toxoplasmosis was made. After this an intradermal toxoplasmin test was applied. The skin test antigen had been prepared from Toxoplasma isolated from a dog with spontaneous canine toxoplasmosis which had been observed previously. A positive reaction was observed after 48 hours. The canine histoplasmin skin test was negative. A serologic test for toxoplasmosis using the method of Sabin and Feldman [1] was positive in a titer of 1:80.

Autopsy Data.—During a course of approximately four and one-half months little improvement was noted, and euthanasia was performed. Autopsy and histopathologic studies confirmed the diagnosis of toxoplasmosis. No evidence of any other disease was found. Pathologic study revealed a chronic diffuse interstitial pneumonitis. The hilar lymph nodes were enlarged and microscopically showed evidence of chronic lymphadenitis, and Toxoplasma could be seen in macrophages. There was pancreatitis, and again some macrophages were seen containing Toxoplasma. The small intestine showed a mucoid enteritis. Individual suspensions of brain, liver, lungs, kidney, heart, spleen, and mesenteric lymph nodes in saline were injected intraperitoneally into mice. Three mice were used for each organ emulsion. Numerous T. gondii organisms were identified in Wright-stained smears of the peritoneal exudate aspirated from mice four and five days after they received the heart emulsion.

The owners of the pet (Mr. and Mrs. J.) were concerned with their health, since they had been in close contact with their pet during its illness. They were referred to the Ohio State University Hospital to determine if there was any evidence of Toxoplasma infection. The skin and serologic tests for toxoplasmosis were negative in Mr. J. However, the studies of Mrs. J. showed evidence of toxoplasmosis and led to the more detailed investigation reported below.

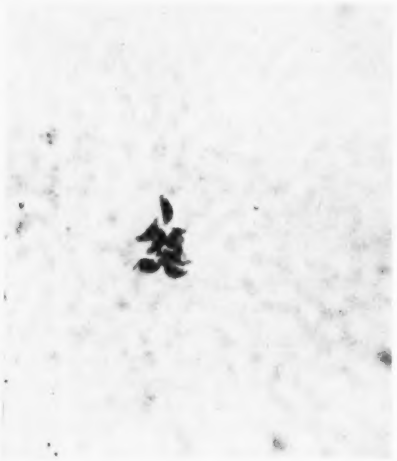
Mrs. J., a 26-year-old childless housewife, had no complaints whatsoever. Careful review of the past medical history revealed nothing of significance.

Physical examination revealed a well-developed well-nourished young woman appearing to be in excellent health. The temperature was 98.2 F., pulse rate 78, respiration rate 14, and blood pressure 130/70. A very thorough examination revealed no deviations from normal except for a

5. Cole, C. R.; Prior, J. A.; Docton, F. L.; Chamberlain, D. M., and Saslaw, S.: Toxoplasmosis: III. Study of Families Exposed to Their Toxoplasma-Infected Pet Dogs, A. M. A. Arch. Int. Med. this issue, p. 308.

small dark brown patch of pigment seen in the retina of the right eye. There was no evidence of any reaction surrounding the pigmented area, and it was the opinion of Dr. Arthur Culler, consultant in ophthalmology, that the area of pigmentation was congenital in origin and not the result of infection with Toxoplasma.

Laboratory Data.—The red blood cell count was 4,190,000; hemoglobin 12.7 gm., and white blood cells count 22,100, with 67% neutrophiles, 29% lymphocytes, 2% monocytes, and 2% eosinophiles. Urinalysis revealed no abnormal constituents. Spinal fluid contained no red or white blood cells, protein 25 mg., sugar 65 mg., and chlorides 685 mg. per 100 cc. Lateral and posteroanterior chest roentgenograms revealed no abnormalities. Roentgenograms of the skull (posteroanterior, anteroposterior, and both lateral views) revealed no organic lesions. The toxoplasmin skin test was positive. Serologic studies, with use of the method of Sabin and Feldman,[1] revealed Toxoplasma antibody titers of 1:80, 1:160, 1:80, and 1:80 on Jan. 25, Feb. 28, April 5, and May 15, 1952, respectively. All titer end-points were duplicated at least once, and controls of known negative and positive serum were included in each test.



Toxoplasmosis recovered by animal inoculation from the blood of Mrs. J. Eight crescentic organisms in Wright-stained smears of mouse peritoneal exudate show the attenuated end, central chromatin body, and chromatin network; × 720.

Five healthy white Swiss mice were inoculated intraperitoneally with citrated blood collected from the patient on Feb. 28, 1952. Three days after inoculation paracentesis of four of these animals revealed abundant peritoneal exudate containing numerous Toxoplasma. All four mice died on the following day. The fifth mouse was shown to be immune to toxoplasmosis when challenged with another strain of Toxoplasma of known virulence. With the same procedure, Toxoplasma organisms were isolated from the patient's blood a second time, on March 4, 1952. We were unable to recover organisms from blood collected on April 5, 1952. Spontaneous infection in the mice was excluded by passage of lung, spleen, liver, and brain emulsions from the same stock. These organisms (designated as the "J" strain) have been serially passed 270 times in mice and 25 times in embryonated eggs. Animal transfer experiments using specimens of sputum, gastric washings, urine, feces, spinal fluid, uterine scrapings, and vaginal secretions yielded no Toxoplasma. After three weeks several mice from each group receiving the above inocula were killed for tissue emulsions and subinoculation into mice and embryonated eggs. The results of the subinoculation were considered negative after 30 days for the mice and 7 days for the eggs.

When the newly isolated ("J" strain) organism was used as the antigen in the Sabin-Feldman dye test, it proved to be antigenically similar to the "RH" canine and porcine strains of Toxoplasma.

CASE 2.—V. F., a 28-year-old white housewife, was admitted to University Hospital on Jan. 5, 1951. She had been apparently well until six weeks prior to admission, at which time she complained of a severe headache. This continued unchecked, and approximately two weeks later she noticed frequent sensations of chilliness and fever. She became disoriented and was taken to a nearby hospital. At that time she had a temperature of 103 F. and was quite irrational and disoriented as to time, place, and person. Spinal fluid contained 196 white cells per cubic millimeter and was reported to be under increased pressure. The patient complained frequently of frontal headache. She lost all ability to identify familiar objects. The family was told that she had "encephalitis," and after four weeks' observation, with no improvement in her mental condition, she was referred to University Hospital. Her past history was noncontributory to her present illness.

Physical examination.—The temperature was 100 F., pulse rate 84, and respiration rate 16. The patient was a well-developed well-nourished woman, lying quietly in bed in no acute distress. She was not oriented as to time or place and did not recognize any members of her family or familiar objects. Examination was essentially negative except for the study of the ocular fundi. There was an albuminous haze in the posterior vitreous of the right eye which obscured most of the fundus; however, the optic disc could be visualized. It was pale, indistinct, and swollen up to 3 diopters. The arteries and veins were greatly narrowed and disappeared within 3 to 4 disc diameters from the disc. The changes were similar but severer on the left, with some evident detachment of the retina. The diagnosis was severe neuroretinitis which was consistent with severe encephalitis, either infectious or toxic, in the opinion of Dr. Arthur Culler, consultant in ophthalmology.

Laboratory Data.—On admission the blood studies showed 3,700,000 red blood cells, 12.5 gm. of hemoglobin, and 5,700 white blood cells, with 38% neurtophiles, 51% lymphocytes, and 11% monocytes. Urinalysis showed no abnormalities. Spinal fluid showed 88 mg. protein per 100 cc., with 14 white blood cells (all lymphocytes) per cubic millimeter. The colloidal gold curve was 5-5-5-5-4-3-2-1-0. Spinal fluid and serum gave negative Kahn and Kolmer reactions. Serologic tests for brucellosis, St. Louis encephalitis, and infectious mononucleosis were negative. The Eastern equine encephalitis complement-fixation test was positive undiluted, and the Western was positive in a dilution of 1 : 2. Subsequent spinal fluid examination revealed proteins to be persistently elevated above normal, with a moderate increase in lymphocytes. The sulfobromophthalein (Bromsulphalein) test was entirely normal. Results of subsequent urinalyses and blood counts were essentially within normal limits. Inoculation of the spinal fluid into mice caused death in five to seven days, and deaths regularly occurred at a similar time in the second and third passages. However, no Toxoplasma organisms were identified.

The skin test with toxoplasmin was markedly positive. The complement-fixation test for toxoplasmosis was reported as positive by Mr. John Bozicevich, National Institute of Health, and the Toxoplasma antibody, as measured by Dr. Harry A. Feldman, of Syracuse University, using the dye test, yielded a titer of 1 : 256.

Treatment and Course.—A diagnosis of toxoplasmosis was made on the basis of the encephalitic manifestations, neuroretinitis, a positive toxoplasmin skin test, and the presence of Toxoplasma antibodies on both the complement-fixation and dye test. Trythrol tetranitrate, 32 mg. every three hours, and nicotinic acid, 100 mg. four times a day, were given in an attempt to dilate the arterioles in the retina. In addition, the patient was given sulfacetamide ,and the blood levels were maintained between 8 and 10 mg. for approximately three weeks.

During the patient's course in the hospital only slight improvement was noted in the ocular fundi, and at the time of her discharge there was still marked impairment of her sight. Further, there was little improvement in her mental status; she was very repetitious, irrational, and totally disoriented. The patient's temperature remained essentially normal most of the time, with only an occasional rise to as high as 100 to 101 F. When seen again, one and two years later, her general physical condition was satisfactory, but there had been no improvement in either her vision or mental condition.

Soon after the patient's admission to University Hospital, her husband stated that he had taken 1 dog, 2 cats, and 12 chickens to the College of Veterinary Medicine for study. Studies of the cats and chickens as well as serum from a cow and a

horse revealed no evidence of toxoplasmosis. Serologic study of the dog serum was positive for Toxoplasma antibodies at a dilution of 1:64, using the Sabin-Feldman dye test. The toxoplasmin skin test was also positive. Observations [6] at this laboratory on experimental toxoplasmosis show that a 1:64 titer in dogs indicates present or past infection.

The dog owned by V. F. was a 1-year-old female Border collie. No visible signs of disease were observed other than emaciation and dehydration. The histoplasmin and coccidioidin skin tests were negative. After 48 hours a 14 by 10 mm. reaction consisting of edema and induration was found at the site of the toxoplasmin test.

No change except weight loss was seen during a period of four month's observation. The dog was killed for pathologic study. Prominent at autopsy were gastritis and enteritis. The enteritis was characterized by extreme ulceration of the duodenum and mucoid inflammation throughout the remainder of the intestine. The mesenteric lymph nodes were large and firm. Several 3 mm. gray foci were seen scattered over the surface of the liver. Cut section of this organ revealed a softened light tan area 2 cm. in diameter. Splenic passive hyperemia and capsular induration were noted. Small nodules were scattered throughout the lungs. The renal capsule was adherent in patches, and white streaks extended into the medulla. No lesions were seen in the cardiovascular, endocrine, nervous, or skeletal systems.

Microscopically, Toxoplasma organisms were seen in lesions of the stomach, liver, myocardium, and mesenteric lymph node.

CASE 3.—C. H., a 2-year-old white girl, was admitted to University Hospital on Dec. 29, 1950, because of a severe paroxysmal cough. Two older siblings had been ill at home for over a month with a similar cough, diagnosed by the family physician as "whooping cough." About three weeks before admission the child began to have a cough which had become progressively more frequent and severer. The paroxysms of cough were frequently accompanied by an inspiratory "whoop" and occasionally were followed by vomiting. On several occasions the family noted that the child became "blue" with severe bouts of coughing. For five days the child had fever, ranging up to 101 to 102 F. The attending physician thought the child had pneumonia complicating pertussis and advised admission to the Ohio State University Hospital.

Past History.—The child had not received any immunizations. According to the mother, the child had had "normal growth and development," but had lost a "little" weight during the present illness. Further inquiry from the mother, who was of limited intelligence, revealed that the child had been given a very high starch diet.

Physical examination revealed a dirty dehydrated 2-year-old girl appearing acutely ill and quite lethargic. Significant findings were injection of the pharynx; enlarged cervical and axillary lymph nodes; rapid grunting respirations with fine inspiratory rales heard over both lungs, more marked posteriorly, especially over the left upper lobe, and tachycardia of approximately 180 beats per minute.

Laboratory Findings.—White blood cell count was 65,600, with 66% lymphocytes, 33% neutrophiles, and 1% eosinophiles; red blood cells count was 4,900,000; hemoglobin was 11.2 gm. Urinalysis showed only a trace of acetone. Wassermann and Kahn tests were negative. Cough plates showed the presence of Hemophilus pertussis. Nose, throat, and stool cultures revealed no pathogenic organisms. On Jan. 5, 1951, white blood cells were 90,200, of which 54% were lymphocytes, 41% neutrophiles, and 5% monocytes. Carbon-dioxide-combining power, blood urea nitrogen, total serum protein, serum albumin, serum globulin, sodium, potassium, chloride, and prothrombin were all within normal limits. A chest roentgenogram showed moderate widening of the upper mediastinum and a mild diffuse hazy infiltrate that radiated from both hila.

Treatment and Course.—On admission the child was given streptomycin, 0.25 gm., and penicillin, 300,000 units, per day. During the next three days the temperature slowly returned to normal, and the patient appeared to be improving. On the sixth hospital day her temperature

6. Docton, F. L.: Serologic Basis for the Diagnosis of Toxoplasmosis in Animals, to be published.

began to rise again, ranging from 101 to 103 F., and the child slowly became stuporous. On the eighth hospital day a lumbar puncture was done. The initial pressure was 110 mm. of water. The spinal fluid contained 33 white blood cells per cubic millimeter, 67% of which were lymphocytes; there were 67 red blood cells per cubic millimeter, and protein was 54 mg. per 100 cc. Spinal fluid sugar and chlorides were normal. With the administration of parenteral fluids the fever subsided to lower levels. The paroxysms continued unchanged, with 8 to 12 severe paroxysms per day. At this time it was found that the child, although 2 years of age, had never spoken, had only a whimpering cry, but the parents believed that she could hear. While in the hospital the child had not spoken and it was not possible to elicit any evidence that she could hear, even in her most alert moments. There was considerable dyspnea at all times requiring continuous oxygen administration. Parenteral fluids were necessary each day to meet body requirements.

On the 15th hospital day the child had a generalized convulsion which was both tonic and clonic. After the seizure had subsided the child would have purposeless flailing movements of the arms and legs, predominately on the left. A chest roentgenogram on the 15th day showed increase in hilar lymphadenopathy and more extensive bronchopneumonia in both lungs. Further widening was noted in the upper mediastinum. Respirations continued rapid and tended to become stridorous. Laryngoscopy was performed on the 16th hospital day and the larynx was found to be inflamed and quite edematous. There was a membranous ulceration on the epiglottis which was shown to be due to Candida albicans. Tracheotomy was performed, and immediately after its completion bronchoscopic examination was made of the lower respiratory tract, which showed only moderate inflammation of the tracheobronchial mucosa.

The convulsive seizure was not repeated, but there was frequent twitchings of the face and purposeless movements of the extremities. Serum sodium, calcium, potassium, and chloride levels were normal at this time. Blood urea nitrogen was 10.5 mg. per 100 cc.; Carbon-dioxide-combining power 66%; red blood cells 4,240,000; hemoglobin 11.6 gm., and white blood cells 20,600, with 66% neutrophiles, 32% lymphocytes, and 2% monocytes. During the following two days there were increasing amounts of mucus aspirated from the trachea, and on the 18th day no breath sounds were heard over the right lower lobe. Bronchoscopy was performed through the tracheotomy and moderate amounts of friable but very tenacious pseudomembrane were found on and about the carina, which could not be removed with the forceps. Large amounts of thick mucus were found in both lower lobe bronchi.

The dyspnea, cyanosis, tachycardia, purposeless movements of the extremities, and twitching of the face became severer, and nystagmus with the rapid component to the left was seen during the last two days of life. The child died on the 18th hospital day.

Autopsy Examination.—The postmortem examination was performed by Dr. W. B. Smith, of the Department of Pathology. On opening the thorax 20 cc. of sanguineous fluid was found in the left pleural space. The lungs were subcrepitant; the right weighed 210 gm. and the left 170 gm. All lobes contained numerous gray-pink nodules about 5 mm. in diameter. The bronchi and trachea contained a moderate amount of pink frothy fluid, and there was a tracheotomy wound just below the larynx.

The spleen weighed 20 gm., and its capsule was thick and purple. The cut section revealed pale pink firm pulp with prominent lymphoid follicles. The pancreas weighed 20 gm., was pink, and had prominent lobulations. The peripancreatic nodes were moderately enlarged and had a pinkish-tan cut surface. The stomach and small and large intestines showed no abnormality, but the mesenteric lymph nodes were enlarged, measuring 3 to 5 mm. in diameter. The liver, gallbladder, adrenals, kidneys, thymus, bladder, ureters, and sex organs showed no gross pathologic changes.

The meninges were thin and membranous. The brain weighed 955 gm. Section of the brain revealed only diffuse congestion of both white and gray matter. The right middle ear contained a small amount of reddish-brown mucoid exudate.

Histopathology.—The heart showed focal myocarditis, with numerous intracellular Toxoplasma organisms. Subacute bronchitis and chronic organizing pneumonia were seen in the lungs. Hyperplasia of the sinusoidal endothelial cells was noted in the spleen. There was perivascular round cell infiltration in the brain, and Toxoplasma pseudocysts were seen within and around focal areas of necrosis and granulomatous inflammation.

The final diagnoses were (1) toxoplasmosis of brain and heart, (2) organizing chronic pneumonitis, (3) subsiding bilateral otitis media, (4) hyperplasia of splenic sinusoid endothelium, and (5) pertussis (clinical).

It was impossible to obtain the cooperation of the family for any correlative search for Toxoplasma infection in the other members of the family or the household pets.

COMMENT

Numerous investigators have considered animals as a probable source of toxoplasmosis in man, since many animals and birds have been found to harbor the infection. Our observation of concurrent human and animal toxoplasmosis may serve to strengthen this contention and to stimulate further investigation of the role of animals as a source of the infection in man.

That there must be asymptomatic Toxoplasma infections in women of child-bearing age to serve as the source of the congenital toxoplasmosis has been assumed on the basis of serologic as well as circumstantial evidence. The finding of a young woman with Toxoplasma parasitemia substantiates this concept. Although we do not have proof that she contracted her Toxoplasma infection from her sick pet, the relationship of active toxoplasmosis in the dog and Toxoplasma parasitemia in the young woman would appear to be more than mere coincidence. Since tonsillitis, pneumonitis, and enteritis were found in the dog at autopsy, dissemination of the Toxoplasma was possible via the sputum, saliva, and feces.

Demonstration of acquired toxoplasmosis in the adult is uncommon. The infection in the young woman with encephalitis is considered to be acquired because of the acute symptoms of recent origin and the high complement-fixation and dye test Toxoplasma antibody titers. Concurrently, her pet dog had toxoplasmosis of the digestive tract, making dissemination of organisms in the vomitus and feces a possible source of her infection.

Further studies should be made on the source of infection for pregnant women who give birth to infected infants.

SUMMARY

Three distinctly different types of Toxoplasma infections in humans are reported. Active toxoplasmosis in two dogs, each associated with an infected woman, is also described. A woman of child-bearing age who had been in close household contact with her Toxoplasma-infected pet dog for four weeks was found to have an asymptomatic Toxoplasma parasitemia. Leucocytosis and Toxoplasma antibody titer (dye test) of 1 : 160 were the only observed deviations from normal.

An acute acquired toxoplasmic encephalitis and neuroretinitis in a young woman whose dog had active toxoplasmosis is reported.

Fatal toxoplasmosis in a child having concurrent severe pertussis is described.

PRIMARY BENIGN PEPTIC ULCERS OF GREATER CURVATURE OF STOMACH

Review of the Literature and Report of Four New Cases

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AND
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HINES, ILL.

THE DICTUM that "all ulcers occurring on or closely adjacent to the greater curvature of the stomach are malignant until proved otherwise" has been accepted in the English literature almost unqualifiedly for the past two decades. Prior to the 1930's very few histologically proved benign greater curvature peptic ulcers had been described, but in those reports it was accepted that the etiology and treatment of these ulcers were the same as for those elsewhere in the stomach. The first published proved case, in 1914, was of a peptic ulcer with chronic perforation into the spleen.[1] In 1925 [2] and again in 1928 [3] reviews were published, revealing only 10 histologically proved cases to that time. Sladký [4] added another case in 1928. In 1931, Sproull,[5] in a discussion of greater curvature ulcers, reported a case which roentgenographically and grossly appeared benign but histologically proved to be a carcinoma. Mathews, in 1935,[6] reported two more benign gastric ulcers and after searching the literature concluded that only 22 peptic ulcers of the greater curvature had been described in sufficient detail to warrant that diagnosis. Of these 22 cases, only 10 had been described in sufficient histological detail. The latter two authors agree with the opinion that was prevalent in that era in which the aforementioned dictum originated. Since 1935, sporadic papers on this subject have revealed 24 proved cases. These reports all attest to the infrequency of these lesions.

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Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are the result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

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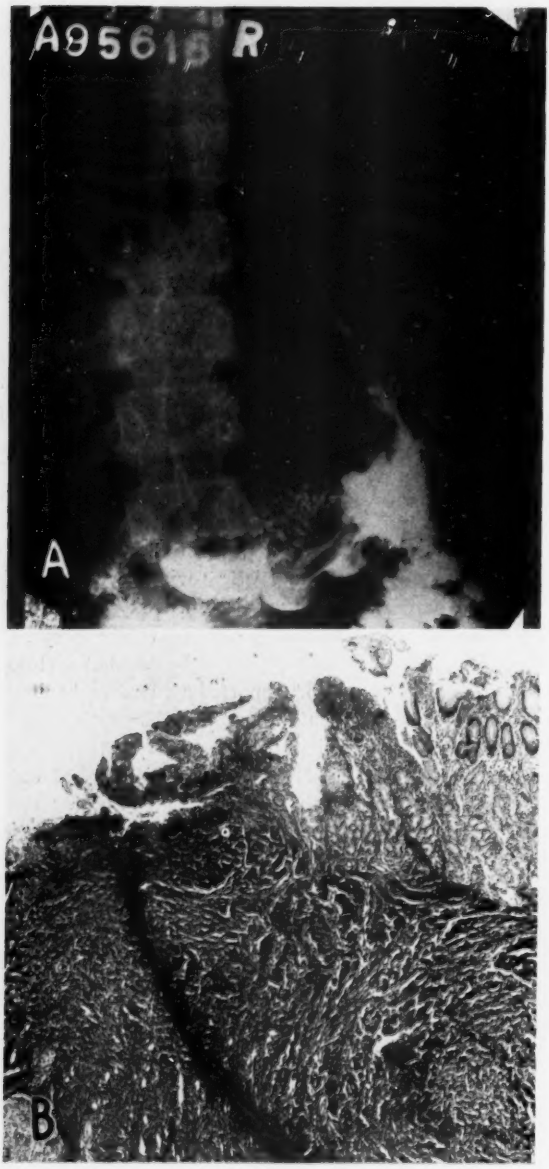

Fig. 1.—*A*, roentgenogram showing area suggestive of ulceration in a prepyloric filling defect. Fluoroscopically this area showed a loss of pliability without any apparent fixation. *B*, microsection of ulcer edge. No evidence of malignancy was noted in multiple sections.

The present review is prompted by two similar cases from the Veterans Administration Hospital, Hines, Ill., occurring recently. A review of the records of the benign gastric ulcers at this hospital for a five-year period, from July, 1947, through June, 1952, revealed two additional cases. During this period 305 patients with benign gastric ulcers were treated at this institution; in 119 of these histologic examinations of the stomach were made, at either surgical or autopsy study.

CASE 1.—W. H. D., a 55-year-old white man, was admitted to this hospital with an established diagnosis of carcinoma of the tongue and complaining of epigastric pain, anorexia, and vomiting. An upper gastrointestinal roentgen series, done soon after admission, showed what was interpreted as an annular filling defect of the antrum (Fig. 1*A*). One week later this patient presented the signs and symptoms of an acute ruptured viscus and underwent emergency abdominal surgery. A 0.5 cm. perforation of the stomach on the greater curvature about 4 cm.

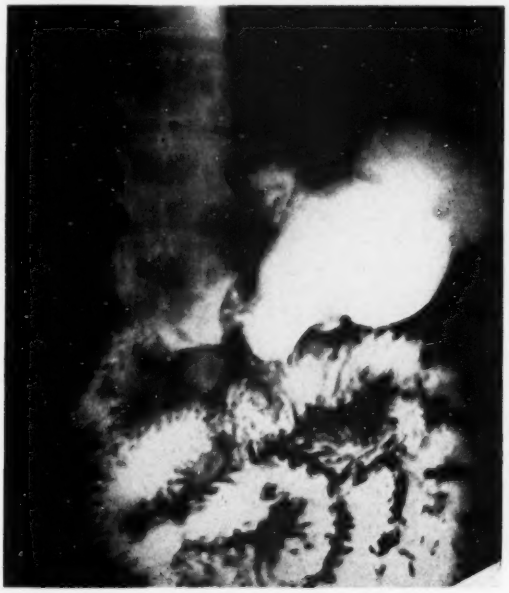

Fig. 2.—Roentgenogram showing ulcer niche on greater curvature of the antrum. The niche does not appear to project beyond the contour of the stomach. On other views, peristalic waves appeared to pass through this area.

proximal to the pylorus was noted and surgically repaired. Palpation of the area of perforation revealed a firm surrounding mass extending along the greater curvature and posteriorly on the stomach. A few small lymph nodes in the gastrocolic ligament were also noted. Postoperatively the patient did very poorly and died 14 hours later.

Autopsy was performed two hours after death. The area of perforation repair in the stomach was noted to be in good condition. Along the greater curvature starting about 2 cm. from the pylorus was noted a round ulcer approximately 4 cm. in diameter. The base was somewhat dirty, and in its center were two small thrombosed blood vessels. Near these vessels was the repaired recent perforation. The mucosa around this ulcer was hypertrophied, congested, and indurated with hypertrophy of the adjacent rugae. Separated from this ulcer by 0.5 cm. of normal mucosa was another small oval ulcer, about 1 cm. long, with the typical base of a benign ulcer. Multiple sections of both ulcers and the adjacent mucosa revealed the typical appearance of a benign ulcer (Fig. 1*B*). Microsection of adjacent lymph nodes revealed merely normal lymph node architecture, without evidence of tumor.

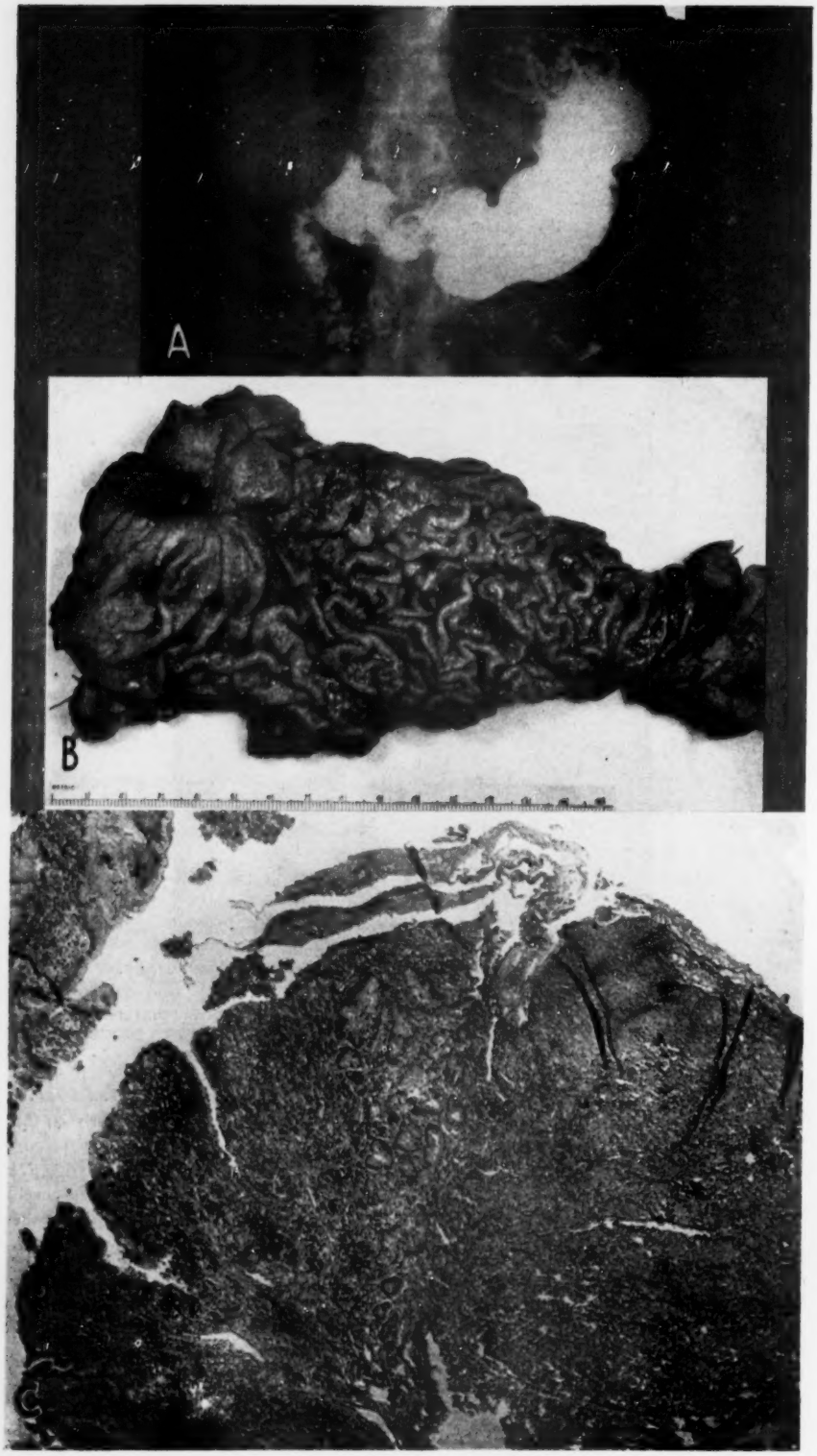

Figure 3

(See legends on opposite page)

Comment.—A case of benign greater curvature gastric ulcer occurring in a patient with an established diagnosis of carcinoma of the tongue is presented. The latter had been recently established and the nutritional status in this patient was good. An acute perforation of the gastric ulcer was repaired but the patient subsequently died. An autopsy proved the benign nature of the lesion in the stomach.

CASE 2.—B. J., a 40-year-old white man, was admitted to the hospital with a diagnosis of recurrent carcinoma of the tongue. He previously had extensive external and interstitial radiation therapy and was admitted to the hospital with extension to contiguous structures. Shortly after admission the patient began to complain of a midepigastric burning type of pain occurring about one hour after meals and relieved by antacids and/or belladonna. Roentgen examination of the stomach revealed a definite ulcer on the greater curvature of the antrum (Fig. 2). Because of the patient's poor nutritional status and the presence of extensive cancer of the tongue he was treated conservatively at this time. Three weeks later a repeat roentgen series showed persistence of the ulcer niche, with very slight decrease in size. Two weeks thereafter, the ulcer niche was noted to have decreased to about half its original size. Because of the persistence of the ulcer after the patient's state of nutrition had been improved and its location, surgery was undertaken. An ulceration of the stomach about 0.5 cm. in diameter, on the greater curvature of the antrum, about 2 cm. proximal to the pylorus, was noted. The surrounding mucosa was firm. A subtotal gastric resection was performed. Histologically the ulcer was noted to be benign. The patient made an uneventful recovery from the surgery. He died three months later from recurrent carcinoma of the tongue and culture-positive pulmonary tuberculosis. Clinically there was no evidence of recurrence of any gastric lesion. No autopsy was performed.

Comment.—In this case also carcinoma of the tongue was an associated condition, as it was in Case 1. In this case, however, the patient's nutritional state was never really good. An autopsy might have contributed additional evidence to validate the benign nature of the gastric ulcer. However, we do feel that the histological proof from study of the surgically resected specimen is sufficient to include the case in the present series.

CASE 3.—L. Mc., a 44-year-old white woman, entered the hospital for the fifth time in January, 1952, complaining of sharp intermittent epigastric pain. This patient had first been seen in 1947, with the complaints of postprandial epigastric pain of eight days' duration. A roentgen series at that time revealed a duodenal ulcer crater and prominence of the antral mucosal folds. Medical therapy was effective in relieving the patient's symptoms, and healing of the crater occurred. Except for occasional mild discomfort, the patient felt well for the following two years, when a severe exacerbation requiring hospitalization occurred. At this time, the fasting gastric contents contained 6 units of free and 22 units of total acid. The patient was again hospitalized in 1951; she had multiple psychosomatic complaints, and note was made that she was aerophagic. Thereafter, the patient adhered rigidly to an "ulcer-type regimen" and was asymptomatic until she reentered the hospital in January, 1952, as mentioned. At this time there was no free acid in the fasting gastric contents but the total acidity was 50 units. A roentgen examination of the upper gastrointestinal tract showed a large crater along the greater curvature of the antrum (Fig. 3*A*). Gastroscopy was subsequently performed. "The antral mucosa was noted to be redundant with large folds running up to and through the very active pyloric ring. A small puckered area with radiating folds running into it was noted on the greater curvature of the antrum, and between this area and the pyloric ring there appeared to be formed a large pouch with each peristalic wave. No ulceration or fixation was noted." Gastroscopic impression

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EXPLANATION OF FIGURE 3

Fig. 3.—*A*, roentgenogram showing large crater along the greater curvature of the antrum. Roentgenographically, this lesion was suggestive of a pseudodiverticulum. *B*, gross specimen showing a large chronically perforating ulcer of the greater curvature. At surgery the ulcer base had to be dissected free of the pancreas. *C*, microsection of ulcer edge. Fibrosis of the wall and lymphocyte and histiocyte infiltration is noted. The bed was composed of a layer of exudate underneath, with a layer of fibrinoid necrosis and fibrosis. There was no evidence of malignancy.

was probably pseudodiverticulum of the greater curvature of the antrum. This examination was repeated by another gastroscopist and essentially the same findings noted. The patient was treated conservatively for three weeks, but because of persistent symptoms and the roentgen findings surgical exploration was advised. At surgery a prepyloric benign-appearing peptic ulcer of the antrum, about 2 cm. in diameter, was found (Fig. 3*B*). Multiple histological sections showed the ulcer to be chronic and benign (Fig. 3*C*), and sections of adjacent lymph

Well-Documented, Histologically Proved Benign Greater Curvature Gastric Ulcers

Date	Author	Sex	Age, Yr.	Location	Follow-Up	Additional Information
1914	Finsterer [3]	M	43	Junction upper and middle thirds of pars media	Not stated	Chronic penetration to spleen
1923	Podlaha [8b]	M	34	Middle third pars media	Not stated	Penetration into spleen
1924	Lorenz [8c]	F	62	Middle third pars media	Not stated	Associated lesser curvature niche present
1924	Lorenz [8c]	F	37	Pars media	Not stated	These two among a series of 115 surgical cases of benign gastric ulcers
1924	von Sommer [8d]	M	37	Pars media	Not stated	Chronic penetration to transverse mesocolon
1927	Simon [8e]	F	33	Pars media	Not stated	.....
1928	Sladký [4]	F	36	Cardia	Not stated	Only case among 128 gastric ulcers operated on
1935	Mathews [6]	F	57	Knee, 12.5 cm. prepyloric	5½ yr.	.....
1935	Mathews [6]	M	57	Pars media, 14 cm. prepyloric	15 mo.	Chronically perforated
1935	Rivers [8h]	F	21	5 cm. prepyloric	Not stated	Chronically perforated
1937	deLuna [8i]	M	53	Upper third pars media	Not stated	.....
1937	Vitols [8j]	M	51	Pars media	1 yr.	Multiple ulcers
1938	Tomoda [8k]	M	52	13 cm. prepyloric	Not stated	Chronic penetration
1938	von Buchem [8l]	M	24	Middle third, pars media	3 yr.	.....
1941	Williams [8m]	F	74	0.5 cm. prepyloric	Died, 3 mo.	Autopsy diagnosis only
1941	Williams [8m]	M	58	6 cm. prepyloric	Died, 2 days	Autopsy diagnosis
1944	Preiss [8n]	M	34	6 cm. prepyloric	None stated	.....
1944	Blum [8o]	M	49	Antral	6 mo.	Associated duodenal ulcer
1946	Tryb [8p]	F	33	Middle third, pars media	None stated	Chronic penetration
1947	Gobeau [8q]	F	53	Distal third, pars media	1 yr.	.....
1947	Hussar [8r]	M	28	Prepyloric	None stated	Gastroscopically benign, associated duodenal ulcer
1948	Campbell [8s]	M	52	Middle third, pars media	None stated	.....
1948	Russell [8t]	M	50	Proximal third, pars media	27 mo.	Chronic penetration
1948	Kennedy [8u]	M	46	Distal third, pars media	3 mo.	Multiple ulcers
1948	Cave [8v]	F	66	7 cm. prepyloric	None stated	Multiple ulcers
1948	Cash [8w]	F	65	Fundus	4 yr.	Chronic penetration
1949	Levin [8x]	M	23	Antral	9 mo.	Gastroscopically malignant
1950	Fierst [8y]	M	32	Antral	3 mo.	Gastroscopically benign
1950	Friedman [8z]	F	65	Distal third, pars media	14 mo.	.....
1950	Friedman [8z]	M	43	3 cm. prepyloric	None stated	Chronic penetration, coexistent lung tumor
1951	Alexander [8a']	F	32	Distal third, pars media	None stated	Associated duodenal ulcer
1951	Holm [8b']	M	40	Middle third, pars media	None stated	.....
1952	Welbourn [8c']	F	24	Distal half of stomach	3½ yr	Multiple ulcers; associated duodenal ulcer, ulcerative colitis, and cirrhosis of the liver

nodes merely showed benign hyperplasia. Postoperatively the patient did well and was seen on follw-up examinations three months later to be without complaints.

Comment.—In this case the ulcer did not show the typical roentgen characteristics of a chronic peptic ulcer. Two gastroscopic examinations were of no help in delineating an ulcer crater, because of an overhanging large mucosal fold extending from the posterior wall. At surgery a chronically perforating benign ulcer, adherent to the pancreas, was found.

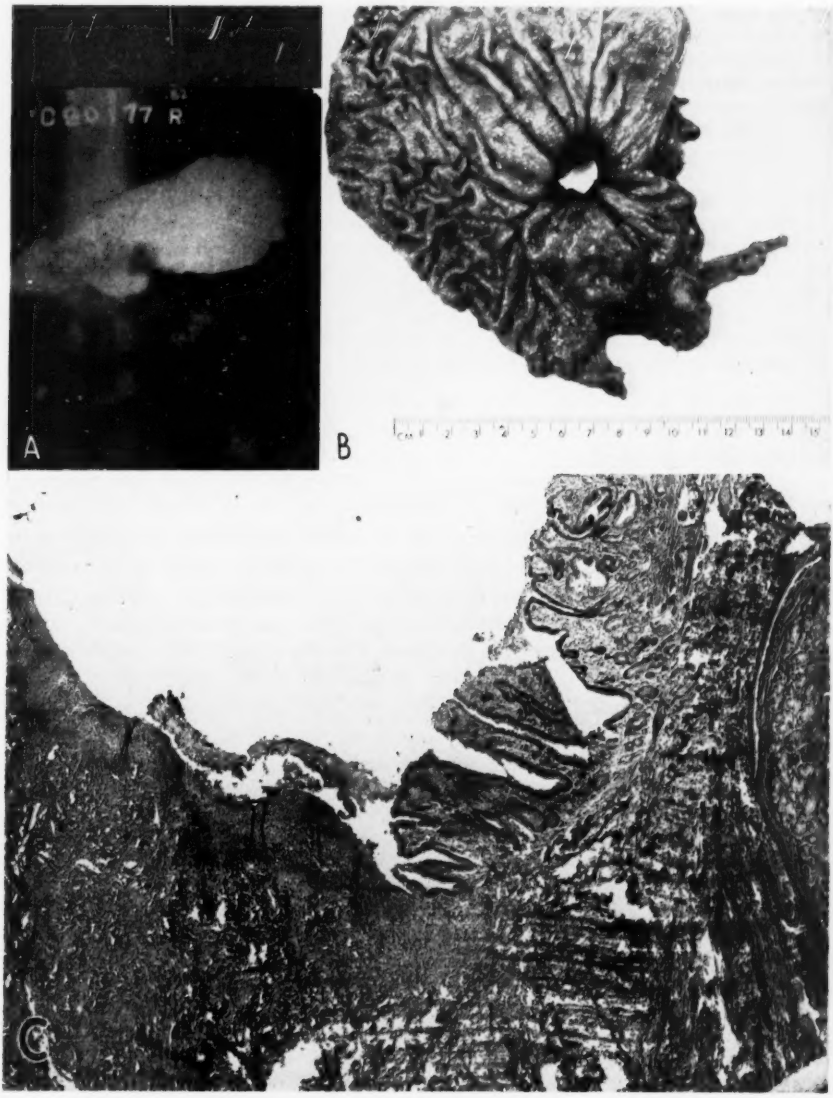

Fig. 4.—*A*, roentgenogram showing large crater on greater curvature of antrum. Radiating folds are well demonstrated. *B*, gross specimen showing large ulcer on greater curvature of distal pars media of the stomach. This lesion was adherent to the anterior and posterior walls of the mesocolon and was thought to be a carcinoma on gross examination. *C*, microsection of ulcer edge. There was no evidence of malignancy.

CASE 4.—J. Nc., a 54-year-old white man, was hospitalized in April 1952, complaining of abdominal distress, nausea, and vomiting. The latter symptoms had been present intermittently for many years but had become more severely acute in the previous 10 days. On admission the patient was noted to be in mild congestive heart failure. The hemogram was within normal limits. A roentgen examination of the stomach revealed a large crater on the greater curvature of the antrum, presumably malignant because of its location (Fig. 4*A*). The fasting gastric contents failed to reveal any free hydrochloric acid. At gastroscopy these findings were noted: "No ulcer crater is visualized but on the greater curvature of the body of the stomach, just proximal to the antrum, a grayish opaque mucus was noted coming down the posterior wall. Peristalsis through the distal half of the stomach is good and no sanguinous material was ever noted during the gastroscopy." Because of persistent symptoms and the roentgen findings, this patient was surgically explored and a subtotal gastric resection was performed. At surgery a large ulcer, 2.5 cm. in diameter, was found on the greater curvature of the stomach, at the junction of the middle and distal thirds of the stomach (Fig. 4*B*). Multiple histological sections revealed the ulcer to be benign (Fig. 4*C*). The patient's postoperative course was uneventful.

The patient was next seen four months later because of mild congestive heart failure and symptomatic osteoarthritis. There were no gastrointestinal symptoms, and roentgen study of the stomach showed a postgastrectomized stomach with a normally functioning gastroenterostomy.

Comment.—In this case the roentgen appearance was typical of a chronic benign peptic ulcer. Again, the lesion was not visualized gastroscopically. Because of the location and mild persisting symptoms surgical exploration was performed.

COMMENT

We believe the greater curvature to be adequately defined as described by Palmer,[7] the greater curvature of the stomach as projected on the posteroanterior profile of the barium-filled stomach. It seems to us to serve no useful purpose to include in this subject only those benign ulcers limited exactly to the area of origin of the omentum as delineated by gross examination of the stomach. By using the roentgenogram as a standard of reference, all the ulcers visualized on the greater curvature would actually be within 1 cm. of either side of the anatomic greater curvature.

In the Table are listed the individual reports of benign greater curvature gastric ulcers found in the literature.[8] All cases accepted by Mathews [6] prior to 1935 are

7. Palmer, E. D.: The Clinical Significance of the Small Benign Gastric Ulcer with a Note on Benign Ulcers of the Greater Curvature and in the Absence of Free Hydrochloric Acid, Am. J. M. Sc. **223**:386, 1952.

8. (*a*) Finsterer and Glaessner.[1] (*b*) Podlaha, J.: The Relation of Chronicity of Gastric Ulcers and Thrombophlebitis Around Gastric Ulcer, Časop. lék. česk. **62**:1380, 1923. (*c*) Lorenz, H. D.: Discussion of the Recognition of Gastric Ulcers of the Greater Curvature, Arch. f. Verdauungskr. **32**:365, 1924. (*d*) von Sommer: Penetrating Ulcer of the Greater Curvature of the Stomach, Klin. Wchnschr. **27**:791, 1924. (*e*) Simon, J.: Ulcer of External Curvature of Stomach, Časop. lék. česk. **66**:1663, 1927. (*f*) Sladký.[4] (*g*) Mathews.[6] (*h*) Rivers, A. B., and Dry, T. J.: Differentiation of Benign and Malignant Gastric Ulcers: Unreliability of Diagnostic Criteria, Arch. Surg. **30**:702, 1935. (*i*) de Luna and Astier: Ulcer of Large Curvature Presenting Aspects of Diverticulum: Case, Bull. et mém. Soc. de radiol. méd. de France **25**:360, 1937. (*j*) Vitols, V.: Multiple Ulcers on the Greater Curvature of the Stomach, Zentralbl. f. chir. **64**:2791, 1937. (*k*) Tomoda, M.: Gastric Ulcer on the Greater Curvature, Zentralbl. f. chir. **65**:2648, 1938. (*l*) von Buchem, F. S. P.: Peptic Ulcer of the Greater Curvature of the Stomach, Brit. J. Radiol. **11**:667, 1938. (*m*) Williams, A. J.: Peptic Ulcer of the Greater Curvature of the Stomach, Radiology **37**:746, 1941. (*n*) Preiss, A.: A Case of Peptic Ulcer on the Greater Curvature of the Stomach, Brit. J. Radiol. **17**:182, 1944. (*o*) Blum, S. D.: Peptic Ulcer of the Greater Curvature of the Stomach, Am. J. Roentgenol. **52**:291, 1944. (*p*) Tryb, R.: Callous Ulcer of the Greater Curvature of Stomach, Lék. listy **15**:277, 1946. (*q*) Gobeau,

(Footnotes continued on next page)

also listed, with one exception. The exception is one of the cases reported by Sladký,[4] in which there was aberrant pancreas at the base of the ulcer. Also the case mentioned by Pancoast in the discussion of Sproull's paper [5] was discounted, because of lack of documentation.

Incidence.—The incidence of benign ulcers occurring on the greater curvature is difficult to determine precisely. In the early literature the incidence varied from 3.5%,[9] based on necropsy records, to 0.7%, of gastric perforations operated on.[1] Lorenz [8c] in a review of three surgical series totalling 1,357 cases noted the over-all incidence to be 3.8%. Portis and Jaffé [10] found from autopsy studies that 2% of 196 gastric ulcers were on the greater curvature. Shackman and Kemp,[11] in 1939, felt that these figures were too high and were due either to changed characteristics of peptic ulcer or to the fact that roentgenology had advanced to such a state that the true nature of greater curvature ulcers could be better delineated. The figures of subsequent reports seem partially to substantiate their contentions. Welch and Allen,[12] in 1948, noted six benign greater curvature ulcers among 512 gastric ulcers operated on, an incidence of 1.2%. Smith and Jordan [13] noted 2 of 211 benign peptic ulcers operated on to be on the greater curvature. Boudreau and his associates,[14] in a necropsy study, found 14% of 168 benign ulcers on the greater curvature. We do not attempt to correlate this last figure with other series in the literature, except to point out that the cases were selected, at least insofar as age is concerned. In our own group of cases, 4 of 119 histologically proved benign gastric

C.; Bonte, G., and Dumez, L.: Three Forms of Ulcer of the Greater Curvature of the Stomach, Arch. mal. app. digest. **36**:632, 1947. (*r*) Hussar, A. E.: Benign Ulcer of the Greater Curvature with Case Report, Gastroenterology **9**:778, 1947. (*s*) Campbell, R. J. C.: Gastric Ulcer of the Greater Curvature; Report of 2 Cases, Brit. J. Radiol. **21**:146, 1948. (*t*) Russell, W. A.: Ulcer of the Greater Curvature of the Stomach; Benign or Malignant? Case Report of Benign Ulcer, Radiology **51**:387, 1948. (*u*) Kennedy, G. R., and Beck, E.: Benign Ulcer of the Greater Curvature of the Stomach, Am. J. Surg. **76**:429, 1948. (*v*) Cave, P.: Benign Ulcers of the Greater Curvature, Brit. M. J. **1**:1185, 1948. (*w*) Cash, S. L., and Marshall, F. A.: Chronic Benign Gastric Ulcer of the Greater Curvature, Rev. Gastroenterol. **15**:821, 1948. (*x*) Levin, E.; Kirsner, J. B.; Clark, D. E., and Palmer, W. L.: Benign Ulcer of the Greater Curvature of the Stomach (Report of Histologically Proven Case), Gastroenteology **13**:166, 1949. (y) Fierst, S. M.; Jones, H. L., and France, S. C.: Benign Ulcer of the Greater Curvature of the Stomach: Report of a Case, Gastroenterology **15**:750, 1950. (*z*) Friedman, R. L., and Epstein, B. S.: Benign Gastric Ulcer of the Greater Curvature, Radiology **55**:398, 1950. (*a'*) Alexander, H. B., and Ballard, W. R.: Benign Ulcer of the Greater Curvature of the Stomach: Case Report, Ann. West. Med. & Surg. **5**:54, 1951. (*b'*) Holm, O. F.: Ulcer of the Greater Curvature of the Stomach, Nord. med. **45**:668, 1951. (*c'*) Welbourn, R. B.: Benign Ulcers of the Greater Curvature Associated with Ulcerative Colitis and Cirrhosis of the Liver, Brit. J. Surg. **39**:303, 1952.

9. Welch, W. H.: Cancer of the Stomach, in System of Medicine, edited by W. Pepper, Philadelphia, Lea Bros. & Co. 1885, V. Z., p. 530. Martin, in System of Medicine, edited by W. Osler and T. McCrae, London, H. Frowde, 1908-1910.

10. Portis, S. A., and Jaffé, R. H.: Study of Peptic Ulcer Based on Necropsy Records, J. A. M. A. **110**:6, 1938.

11. Shackman, R., and Kemp, F. H.: Chronic Ulceration of the Greater Curvature of the Stomach with a Case Report, Brit. J. Surg. **27**:316, 1939.

12. Welch, C. E., and Allen, A. W.: Gastric Ulcer, New England J. M. **240**:277, 1949.

13. Smith, F. H., and Jordan, S. M.: Gastric Ulcer: A Study of 600 Cases, Gastroenterology **11**:575, 1948.

14. Boudreau, R. P.; Harvey, J. P., Jr., and Robbins, S. L.: Anatomic Study of Benign and Malignant Gastric Ulcerations, J. A. M. A. **147**:374, 1951.

ulcers occurred on the greater curvature, an incidence of 3.3%. However, our series is too small to have any statistical significance. If, however, we accept the figure of 1%, from the cited statistics, as average for the occurrence of greater curvature benign ulcers, there still remains a gross discrepancy between this figure and the fewer than 40 documented reports in the literature. Many cases, undoubtedly, have been included in surgical series of benign gastric ulcers. Rarely, in such reports, have the individual cases of greater curvature ulcers been documented. Because of the failure of documentation, such cases have not been included in the present review. One may speculate about the existence of other proved cases which have not been written up for the medical literature.

Another approach to the incidence is the question: How many greater curvature ulcers are malignant and how many are benign? We mean to distinguish here between the malignant ulcer and the ulcerating carcinoma. The advance of roentgenology has been such that, with the use of mucosal-pattern and pressure-spot techniques, this distinction can be fairly well made.[15] Admittedly the ulcerating lesion which contains a small rim or edge of malignancy is still a difficult diagnostic problem to the radiologist, often even to the pathologist. In a previously cited statistical study of 258 proved cases of gastric ulceration [18] 5 ulcers were found on the greater curvature. Three of these were malignant. We have reviewed our own cases of gastric carcinoma for the same five-year period, July, 1947, through June, 1952, as was previously reviewed for benign gastric ulcers. Of 436 cases of gastric carcinoma, in 52 there were roentgenograms which showed the lesion to be primarily ulcerative. In only three of these cases did the lesion occur within the limits of the greater curvature as defined by us. When we totaled our figures, we find that 171 proved cases of gastric ulceration were noted on roentgenographic examination at this hospital for a five-year period. Seven of the ulcerations occurred on the greater curvature, and of these four were benign.

Differential Diagnosis.—Syphilis, congenital or acquired, may mimic chronic peptic ulcer, particularly when a submucosal gumma breaks down with ulceration. The clinical symptomatology may simulate peptic ulceration, but more frequently suggests gastric carcinoma, with immediate postprandial pain and weight loss. The positive diagnosis of gastric syphilis is frequently quite difficult and usually debatable.[16] The rapid response to specific antisyphilitic therapy is strong presumptive evidence of this diagnosis.

Tuberculosis of the stomach may also simulate chronic peptic ulcer. Clinically and roentgenographically tuberculous ulceration is practically indistinguishable from chronic peptic ulcer.[17] Gastroscopically and grossly, the ulcer has undetermined edges, a serpiginous outline, there are frequent nearby superficial tubercles, and there is usually little interference with gastric motility.[18] The lesion is usually associated with tuberculosis elsewhere in the body. The histological features, of course, serve to distinguish the lesion from simple peptic ulcer.

15. Baker, L.; Grovett, E. A., and Spellberg, M. A.: Diagnostic Accuracy of Gastroscopy in Neoplasms of the Stomach, Cancer **5**:1116, 1952.

16. Palmer, W. L.: Textbook of Medicine, edited by Cecil and Loeb, Philadelphia, W. B. Saunders Company Ed. 8, 1951.

17. Clagett, O. T., and Walters, W.: Tuberculosis of the Stomach, Arch. Surg. **37**:505, 1938.

18. Palmer, E. D.: Tuberculosis of the Stomach and the Stomach in Tuberculosis, Am. Rev. Tuberc. **61**:116, 1950.

A crater may be simulated by a mucosal pocket in an area of hypertrophic gastritis. Severe ulcerative antritis may produce actual ulceration of the greater curvature. The ulceration here is a secondary phenomenon and we are, by definition, eliminating these lesions. In hypertrophic gastritis a single pocket amid swollen rugae is like a small ulcer, but the involved wall is elastic and mobile and there is no evidence of retraction by fibrosis.

Gastric diverticulae may simulate ulcer craters but are extremely uncommon along the greater curvature. In a collective review of 342 cases, only 5% were located on the greater curvature, while 76% were at the usual location, high on the posterior wall adjacent to the lesser curvature and just beyond the esophago-

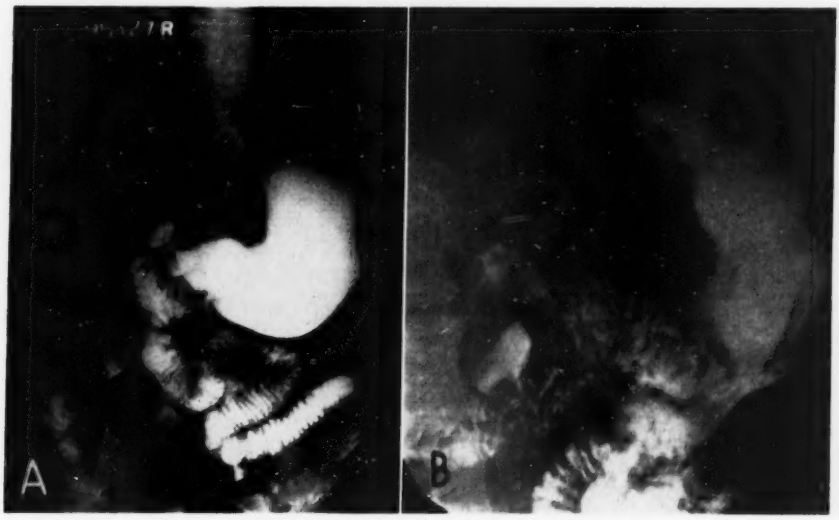

Fig. 5.—*A*, roentgenogram showing what was interpreted as ulcer crater of greater curvature. *B*, repeat examination two months later showing normal antrum, deformed duodenal bulb, and diverticulum arising in the region of the duodenojejunal junction.

cardiac junction.[19] The adjacent stomach wall is normal unless secondary changes are present.[20] Pseudodiverticulae of the greater curvature, due either to a previous peptic ulcer with chronic perforation and blind fistula formation or to ulceration of aberrant pancreas or schwannomas, may occur.

Another pitfall in the differential diagnosis of greater curvature ulcer involves lesions of the duodenojejunal loop seen on cursory roentgen examination. We recently had occasion to see such an instance.

G. P., a 54-year-old white man, was admitted to the hospital in congestive heart failure. Among other complaints there were symptoms of postprandial burning epigastric distress and moderate weight loss. A roentgen examination of the stomach revealed what was interpreted as an ulcer of the greater curvature of the antrum, presumably malignant by reason of its location

19. Palmer, E. D., Collective Review; Gastric Diverticula, Internat. Abstr. Surg. **92**:417, 1951, in Surg., Gynec. & Obst. 1951

20. Bralow, S. P., and Spellberg, M. A.: Diverticula of the Stomach: Report of 26 New Cases, Gastroenterology **11**:59, 1948.

(Fig. 5*A*). The patient received no antacid medication and continued to have distress. At this time, because of the persistent clinical symptomatology and the roentgen findings, it was recommended that an exploratory laparotomy be performed with the view of doing definitive surgery for a probable gastric carcinoma. This, however, was delayed because of the patient's very poor cardiac status. During this interval, the primary etiology of the congestive heart failure was determined to be a "marked hyperthyroidism." At the same time, antacid medication was instituted, with prompt relief of the patient's gastrointestinal complaints. Gastroscopy was performed, and no ulcer crater was visualized. A second roentgen examination was now performed and showed only a duodenal bulb deformity and diverticulum of the fourth part of the duodenum (Fig. 5*B*). A review of the original stomach roentgenograms revealed that the originally described antral ulcer was most likely the duodenal diverticulum superimposed, in the roentgenogram, on the greater curvature of the antrum.

Treatment.—We do not intend to discuss the relative merits of surgical or medical therapy of gastric ulcers. However, we do believe that the decision as to the type of treatment to be instituted need not of necessity rest primarily on the location of the ulcer. We appreciate the difficulties met with in the prepathological diagnosis of ulcers anywhere in the stomach, but we do not feel that the mere particular location on the greater curvature precludes the diagnosis of benign peptic ulcer. Although the generally accepted treatment of greater curvature gastric ulcers today is surgical,[21] we should like to point out that some of these ulcers are completely benign. Because of the rarity of such benign ulcers, the publication of well-documented cases should be encouraged. We must agree with Mathews,[6] among others, that all such cases have histological proof. It is also well to be aware of reports of gastric ulcers thought to be benign but found to be malignant after exhaustive studies of multiple histological sections of the lesion.[22] Because of this and other documented reports of healing of malignant ulcers of the stomach,[23] it is preferable that in such cases a follow-up study be made after two or three years.

SUMMARY

The literature is reviewed and 33 well-documented and histologically proved primary benign peptic ulcers of the greater curvature of the stomach are listed; to these are added 4 additional case reports.

A discussion of incidence, differential diagnosis, and pitfalls in diagnosis of primary benign peptic ulcers of the greater curvature of the stomach is presented.

A suggestion is forwarded for reconsideration and reevaluation of the dictum "greater curvature gastric ulcers are malignant until proved otherwise."

Dr. Lyle A. Baker, Chief, General Medical Service, assisted in preparation of the manuscript and members of the resident staff assisted in the translation of the foreign language articles.

21. Ferreira, A. E. M., and de Sousa, A.: A Case of Chronic Ulcer of the Greater Curvature of the Stomach Simulating Carcinoma, Gaz. méd. port. **3**:111, 1950.

22. Harynkiewytsch, T.: Differential Diagnosis of Greater Curvature Ulcers of the Stomach, Forthschr. Geb. Röntgenstrahlen **71**:906, 1949. Sproull.[5] Shackman and Kemp.[11] Ferreira and de Sousa.[21]

23. Palmer, W. L., and Humphreys, E. M.: Gastric Carcinoma: Observations on Peptic Ulceration and Healing, Gastroenterology **3**:257, 1944. Grimes, O. F., and Bell, H. G.: Clinical and Pathologic Studies of Benign and Malignant Gastric Ulcers, Surg., Gynec. & Obst. **90**:359, 1950.

TREATMENT OF PNEUMOCOCCAL PNEUMONIA WITH ERYTHROMYCIN AND CARBOMYCIN (MAGNAMYCIN)

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WITHIN the past nine months two new antimicrobial agents, erythromycin and carbomycin (Magnamycin), have been described and preliminary reports of their clinical use have been published.[1] Each has been shown to have in vitro activity of a high order against most Gram-positive bacteria, including the pneumococci. A small study was undertaken, therefore, to test the efficacy of both agents in the initial management of adult patients with proved pneumococcal pneumonia. This report describes the results of the administration of erythromycin to 12 and carbomycin to 8 persons with pneumonia. The series was not enlarged because the results of therapy in both groups were so unsatisfactory that further study was precluded.

METHODS AND MATERIALS

The 20 unselected patients were treated in the general medical wards of the Syracuse Medical Center Hospitals and received similar accessory medical and nursing attention. Infection in the group as a whole was not unusual (Table 1). Pneumococci were isolated by smear and/or culture from initial sputum of each patient, and the pneumococci were the predominating organisms in all. Six patients (30%) had initial bacteremia. Each patient had roentgenographic evidence of lobar or segmental consolidation typical of bacterial pneumonia. In six of the patients two lung lobes were involved although in no instance was the second lobe seen to be completely consolidated by roentgen examination. The 20 patients presented clinical pictures compatible with pneumonia. Fifteen were acutely ill, and five were critically so. The average age of the entire group was approximately 50 years; those in the carbomycin series averaged 16 years older than those in the erythromycin series. At the time of hospital admission

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Erythromycin was supplied by The Upjohn Company, Kalamazoo, Mich., and Abbott Laboratories, North Chicago, Ill. Magnamycin was supplied by Chas. Pfizer & Company, Inc., Brooklyn.

1. (*a*) Haight, T. M., and Finland, M.: Antibacterial Action of Erythromycin, Proc. Soc. Exper. Biol. & Med. **81**:175-183 (Oct.) 1952; (*b*) Laboratory and Clinical Studies on Erythromycin, New England J. Med. **247**:227-232 (Aug. 14) 1952. (*c*) English, A. R.; Mullady, H. E., and Fitts, R. A.: Magnamycin (Carbomycin): II. In Vivo Studies, Antibiotics & Chemother. **3**:94-98 (Jan.) 1953. (*d*) Welch, H.; Randall, W. A.; Reedy, R. J., and Kramer, J.: Bacterial Spectrum of Erythromycin, Carbomycin, Chloramphenicol, Aureomycin and Terramycin, ibid. **2**:693-696 (Dec.) 1952. (*e*) Josselyn, L. E., and Sylvester, J. C.: Absorption of Erythromycin, ibid. **3**:63-66 (Jan.) 1953. (*f*) English, A. R.; Field, M. F.; Szendy, S. R.; Tagliani, J., and Fitts, R. A.: Magnamycin: I. In Vitro Studies, ibid. **2**:678-688 (Dec.) 1952.

14 of the patients had rectal temperature above 103 F.; temperature of the others was above 100 F. Sixteen had leucocytosis (cell count above 15,000 per cubic millimeter), and only one patient had a normal white blood cell count. Five of the 20 patients were in congestive heart failure and/or were alcoholic. No instance of a purulent complication was encountered before therapy.

In the 20 patients pneumonia had existed for from one to seven days prior to hospitalization and specific therapy. The average duration of illness was 2.9 days in the 16 patients who clearly identified its onset. In the four remaining patients the onset could not be dated precisely, and in each one suggestive symptoms had been present for approximately one week prior to admission.

Dosage of erythromycin, administered orally to 12 patients, ranged from 1.2 to 2 gm. daily; four patients were given 1.2 gm., and six received either 1.5 to 1.6 gm. Total daily dosage was equally divided into from four to six doses of 200 to 500 mg. each. No effort was made to administer single doses to conform with or to avoid meals. Carbomycin was administered by both the oral and intramuscular routes. Two patients received 1.5 and 2 gm. intramuscularly, divided into three or four doses of 500 mg. Oral dosage of carbomycin in the other six ranged from 1.25 to 2 gm. daily, divided into three or four doses. Both agents were administered in gelatin capsules, and no enteric coating was added to the capsules.

TABLE 1.—*Clinical Characteristics on Admission of Twenty Patients with Pneumococcal Pneumonia Treated with Erythromycin or Carbomycin (Magnamycin)*

	Patients, No.	
	Erythromycin Series (12)	Carbomycin Series (8)
Pneumococci in sputum	12	8
Bacteremia	3	3
Younger than 50 yr.*	7	2
Older than 50 yr.*	5	6
Pneumonia in 2 lobes	3	3
Critically ill	1	4
Acutely ill	11	4
Hyperpyrexia (above 103 F.)	8	6
Leucocytosis (above 15,000/cu. mm.)	10	6
Associated alcoholism and/or heart failure	3	2

* The average age of the patients in the erythromycin series was 46 yr.; in the carbomycin series it was 62 yr.

Duration of therapy with the two agents ranged from 1 to 12 days. Seven patients received from 7 to 9 days' continuous treatment, three were treated for from 10 to 12 days, and three for 5 or 6 days. Because the clinical course warranted it, therapy of the remaining seven patients was changed to administration of penicillin 24 to 120 hours after institution of treatment with erythromycin or carbomycin (three of these patients were in the erythromycin series). In no instance was it necessary to interrupt therapy with either erythromycin or carbomycin because of untoward side effects.

RESULTS

Combined roentgenographic, bacteriologic, and clinical responses to therapy with erythromycin and carbomycin were satisfactory in 9 of the 20 patients (45%), as shown in Table 2; 5 were in the erythromycin series and 4 in the carbomycin group. Among these nine patients no difference in responses could be demonstrated between those who received carbomycin and those who received erythromycin. In each case there was an abrupt fall of temperature to below 100 F., with accompanying signs of amelioration of the infection. Roentgenographic clearing was completed by the third week in all. Figure 1 represents the clinical course of one of these nine patients.

H. C., a 63-year-old white man, who was an unemployed laborer, entered the hospital with a 48-hour history of recurrent shaking chills, high fever, productive cough, and severe pleuritic

pain over the entire left anterior chest. On examination he was found to be critically ill, cyanotic, dyspneic, in obvious pain, and coughing frequently. Signs of consolidation were demonstrated over the left upper lung lobe and over the apical portion of the left lower lobe. Characteristic rusty sputum contained Type 3 pneumococci, and there was a leucocytosis, with a white cell count of 16,000. The blood culture was sterile. Within 28 hours of instituting therapy with carbomycin (1.5 gm. daily, orally) there was an abrupt clinical and febrile crisis. The remission of all signs of infection was maintained, and roentgenograms 7 and 14 days later revealed the rapid and complete clearing of the parenchymal infection.

Resolution of the pulmonary consolidation was delayed beyond 21 days in five patients; four of them were in the erythromycin group (Table 2). The designation of "delayed resolution" was arbitrarily chosen and was used to indicate any residual clinical or roentgenographic evidence of the process later than three weeks after institution of treatment. Eventual complete recovery occurred in all five patients between the fourth and sixth week after onset of the pneumonia. In the four patients

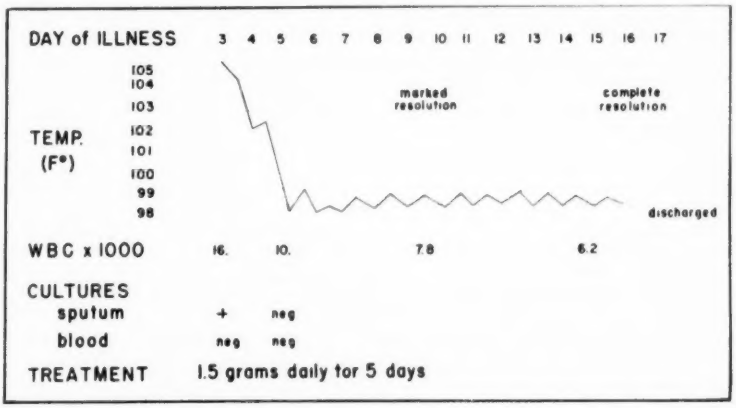

Fig. 1.—Treatment with carbomycin of pneumococcic pneumonia with consolidation in the left upper lobe in H. C., a 63-year-old white man. The positive sputum culture contained Type 3 pneumococci.

treated with erythromycin, therapy was changed to use of penicillin after from six to nine days. In none of these was this change followed by more rapid clearing of the roentgenogram or by improvement in the clinical picture. In two of the four patients intrapleural collections of fluid developed during the course of their illness, as demonstrated by x-ray. These occurred after the fourth day of treatment, were not aspirated, and resolved completely. Carbomycin was continued for 10 days in the single patient in that series in whom resolution was prolonged. Subsequent therapy with penicillin again failed to alter the course of this patient's infection. Although a complicating lung tumor was suspected in all five patients, none was proved; bronchoscopy was done in three patients during the period of hospitalization.

Three patients treated with erythromycin and three patients treated with carbomycin failed to respond in a satisfactory manner, and a change in therapy after one to four days was considered necessary (Table 2). There were two deaths, both in the erythromycin series.

A white man aged 65 entered the hospital on the third day of his acute illness. He had left upper lobe consolidation and some involvement in the left lower lobe and was in mild congestive heart failure. He was given 2 gm. of erythromycin daily. For the first 48 hours of therapy there was no appreciable effect upon fever or clinical course, and he remained acutely ill. Following the laboratory report that the 48-hour blood culture was still positive for pneumococci (New York State Pool 2), penicillin was prescribed, after the 60th hour. There was some temporary improvement within the next 48 hours, but a pleural effusion appeared, and on the sixth day of therapy (ninth day of illness) thoracentesis revealed that the intrapleural fluid had changed to pus, which was sterile on culture. Gradual deterioration in health followed, and the patient died on the eighth day. Autopsy revealed a large acute lung abscess, massive empyema, and an active pneumonic process in both upper and lower lobes on the left.

The other patient who died was a 72-year-old woman; she died on the 20th day of hospitalization. The pneumococci recovered initially from sputum were not typed. The pneumonia was in the right lower lobe, and the patient had no serious associated preexisting disease. With therapy there was defervescence to normal in 24 hours and some clinical improvement. A secondary rise in temperature occurred at the 60th hour, and fever, between 100 and 101 F., persisted thereafter. Pleural effusion was first noted on the fifth day of treatment, and therapy with penicillin was started at that time. In the next 14 days there was gradual improvement in the

TABLE 2.—*Clinical Results of Therapy with Erythromycin and Carbomycin in Twenty Patients with Pneumococcal Pneumonia*

	Patients, No.			
	Erythromycin Series (12)		Carbomycin Series (8)	
Clinical response satisfactory	5		4	
Clinical response unsatisfactory	3*		3	
No clinical or bacteriological effect within 96 hr.		1		1
Extension of disease on 4th day of treatment		0		1
Empyema on 4th-6th day of treatment		2		1
Slow but complete resolution	4†		1	
Number treated with penicillin after 2 to 5 days	3		4	

* Two of these patients died after 8 and 20 days, one with empyema; the clinical course of the other was unaffected.

† In two of these patients pleural effusion developed after the third treatment day.

clinical picture and roentgenograms revealed slow resolution of the lung infection. The patient died suddenly on the 20th day of illness, and at autopsy a septic embolus to the superior mesenteric artery was found. Pneumonia in the right lower lobe was organizing, and no organisms were cultured from it.

A third patient failed to respond satisfactorily when treated with erythromycin.

Forty-eight hours after institution of therapy with 1.2 gm. of erythromycin daily, the sputum of the patient, a 76-year-old woman, contained more pneumococci than were present on the initial specimen and the cultures were still positive. Because there had been no effect upon the temperature, which had remained above 103 F., or upon the acuteness of the clinical illness, therapy was continued, thereafter, with penicillin. With this treatment there was a prompt clinical and febrile crisis within 30 hours, and the patient made an uneventful recovery, although resolution was not complete until the sixth week of illness.

Therapy with magnamycin was unsatisfactory in three patients (Table 2).

The first was a 45-year-old Negro man, acutely ill with pneumococcal pneumonia (New York State Pool 2) in the right middle lobe. With 1.5 gm. of carbomycin daily the initial bacteremia cleared, but the sputum culture was still positive for pneumococci at 48 hours. The temperature, after an abrupt fall to 100 F., within 30 hours rose again to 103 F. on the fourth day, and clinical evidences of relapse developed. An extension of the disease to the right lower

lobe, with the development of a large pleural effusion, was discovered. Use of penicillin was started, and there was prompt and impressive improvement within 48 hours. Complete cure of the infection occurred by the fifth week of illness.

The second patient, a 62-year-old woman, with an initial bacteremia treated with carbomycin, was more seriously ill at the end of 48 hours than on admission. Her blood and sputum cultures were still positive for Type 7 pneumococci, her temperature was above 103.5 F., and she remained cyanotic. Penicillin was given, and she responded satisfactorily thereafter. Recovery was completed by the fifth week of illness.

The third failure with carbomycin occurred in a 43-year-old Negro man, an alcoholic, who had Type 3 pneumococcal pneumonia in the left lower lobe, with bacteremia (Fig. 2). With treatment, 2.0 gm. of carbomycin daily given parenterally, there was a febrile crisis within 30 hours and marked associated clinical improvement. The patient's course for the next two days was satisfactory. On the third day of treatment there was a clinical relapse, with recurrence of fever, the development of a large left pleural effusion, and extension of the disease into the left upper lobe. Blood cultures taken at the 48th hour were reported positive at this time,

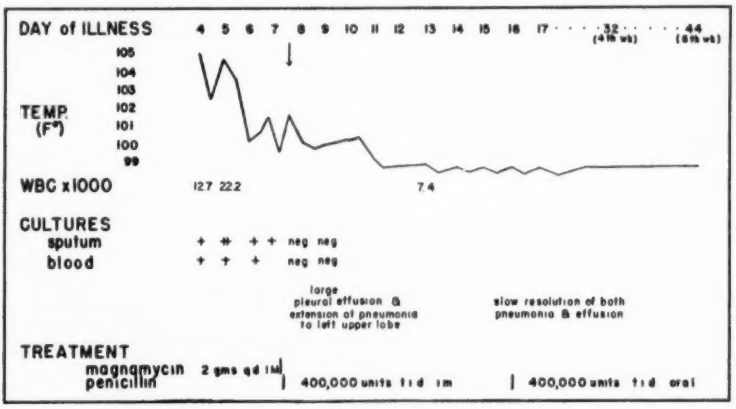

Fig. 2.—Treatment with carbomycin (Magnamycin) of pneumococcic pneumonia with consolidation in the left lower lobe in L. W., a 43-year-old Negro man. The positive sputum and blood cultures contained Type 3 pneumococci.

the sputum still contained culturable pneumococci, and medication was changed to penicillin. Slow improvement and cure, both clinical and roentgenographic followed.

Therapy with carbomycin was discontinued after the seventh day in one other patient because of the persistence of low grade fever following an initial febrile crisis (Table 2). Penicillin failed to alter the temperature course in this patient, however, and the disease eventually cleared in 21 days.

The three failures with carbomycin occurred in the three youngest patients in the series of eight. Two of the three were alcoholics, but there was no important associated disease in the oldest. In the erythromycin series, each of the three patients whose course was unsatisfactory had evidences of arteriosclerotic heart disease but only one was in congestive failure. The most impressive clinical responses to therapy in this group took place in the youngest and the least ill.

Table 3 depicts the response of fever to treatment in the two groups. In the erythromycin group the temperature of 9 of the 12 patients dropped to 100 F. or below within 60 hours, and in 8 of these 9 it dropped within 48 hours. In a tenth

patient the temperature fell gradually over a 96-hour period. In two other patients therapy had no appreciable effect upon the initial hyperpyrexia. In four of the nine patients whose initial defervescence was satisfactory fever recurred after the fourth day and persisted at levels above 100.5 F. for periods longer than 72 hours. In two of them the recurrence of fever was associated with other evidences of clinical relapse, as described above. Fever in six of the eight patients treated with carbomycin fell to near normal in 60 hours, and in five of these within 48 hours. Gradual decrease of fever took place in one patient, and in another there was no appreciable effect upon fever. Two of the six patients had a febrile relapse after the 72d hour, which persisted for more than three days.

TABLE 3.—*Response of Fever to Therapy with Erythromycin and Carbomycin*

	Patients, No.	
Time of Defervescence to Below 100 F., Hr.	Erythromycin Series (12)	Carbomycin Series (8)
18-30	6	3
30-60	3	3
60-96	1	1
No effect upon fever	2	1
Initial defervescence followed by recurrence of fever (to 100 F. or higher) which persisted longer than 72 hr.	4	2

TABLE 4.—*Bacteriological Results in Twenty Patients with Pneumococcal Pneumonia Treated with Erythromycin and Carbomycin*

	Patients, No.	
	Erythromycin Series (12)	Carbomycin Series (8)
Initial bacteremia	3	3
Persistent positive blood cultures 24 or more hours after start of treatment	1	2
Persistent positive sputum culture for pneumococci 48 or more hours after start of treatment	2	2
Sputum and blood cultures sterile after 24 hours of treatment	9	5

Bacteriological results of therapy are shown in Table 4. Initial bacteremia was present in six patients (30%), three in each series. Blood culture of one patient treated with erythromycin was positive for pneumococci after 48 hours. Blood cultures of two patients treated with carbomycin were positive after 24 and 48 hours. In four instances (two in each series) pneumococci were found by both smear and culture of sputum after 48 or 72 hours. Sputum and blood cultures of 14 patients became sterile within 24 hours, 9 treated with erythromycin and 5 treated with carbomycin.

COMMENT

These few observations upon 20 subjects indicate clearly, to the authors at least, that erythromycin and carbomycin can not and should not be considered as effective agents in the therapy of pneumococcal pneumonia. The inevitable conclusion is that penicillin, aureomycin, chloramphenicol, and oxytetracycline (Terramycin) are far more efficacious drugs in the treatment of this acute infection than either

erythromycin or carbomycin.[2] Indeed it seemed to us that further therapeutic trials with either drug were both unwarranted and probably dangerous.

This is a reasonable decision because, as a group, the 20 patients presented no unusual picture of pneumococcal pneumonia, and proper response to therapy in each was anticipated. Actually, they were, as a whole, less ill than patients in previously described series.[2d,e] Five of the 20 were critically ill on admission, but no one was moribund. No patient had a purulent complication upon admission to the hospital. There was only one instance of gastric dilatation or ileus, and the patient with this condition received carbomycin parenterally. No patient was in or near shock. Although there were three alcohol addicts, only one was truly intoxicated upon hospital admission and none had cirrhosis. Mild to moderate, but not severe, congestive heart failure was present in three. The average age of the patients in the carbomycin-treated group was high, but each of the eight was in reasonably good general health immediately prior to onset of the pneumonia. Finally, in no instance was a mixed pulmonary infection present, from either a clinical or a bacteriological standpoint. Thus the disease in the two groups as a whole, and in each individual, was not of unusual severity.

It is possible, with the dosage used and with the gelatin capsules given without concern about the physiological condition of the stomach, that insufficient amounts of both erythromycin and carbomycin were prescribed. Because blood concentrations and sensitivities of the organisms were not measured, no data can be offered to eliminate the possibility. According to all available reports, however, the regimens employed were presumably sufficient, and they certainly were greater than those generally recommended.[3] Furthermore, no pneumococci have been found to date which have been resistant initially to either drug.[4] It must be emphasized, therefore, that if good clinical results can be expected from either drug only upon their prescription at certain times and with special carrying agents, or upon knowledge of the organism's sensitivity to them, then the margin of their safety is insufficient for practical use in pneumococcal pneumonia.

It is not the purpose of this report to compare the efficacy of erythromycin with that of carbomycin in the treatment of patients with pneumonia, and it would be impractical to make the comparison with only 12 and 8 patients, respectively, being treated with the two agents. It is apparent that the patients in the carbomycin series were older and were probably, as a whole, more seriously ill than those in the erythromycin group, at least as evidenced by the increased incidence of bacteremia (3 of 12 compared with 3 of 8). From data shown in Tables 2, 3, and 4 it is obvious that the results of therapy with carbomycin were less impressive than

2. (*a*) Dowling, H. F., and Lepper, M. H.: Effects of Antibiotics (Penicillin, Aureomycin, Terramycin) in Fatality Rates and Incidence of Complications in Pneumococcic Pneumonia, Am. J. M. Sc. **222**:396-403 (Oct.) 1951. (*b*) Kirby, W. M. M.; Michel, J. C.; Coleman, D. H.; Haviland, J. W., and Sparkman, D. R.: Comparison of Aureomycin and Chloramphenicol in the Treatment of Bacterial Pneumonia, J. A. M. A. **147**:110-115 (Sept. 8) 1951. (*c*) Knight, V.: Clinical Evaluation of Aureomycin, Chloramphenicol and Terramycin, New York J. Med. **50**:2173-2181 (Sept. 15) 1950. (*d*) Bunn, P. A.; McDermott, W.; Hadley, S. J., and Carter, A. C.: Treatment of Pneumococcic Pneumonia with Orally Administered Penicillin, J. A. M. A. **129**:320-327 (Sept. 29) 1945. (*e*) Bunn, P. A.: Present Trends in the Treatment of the Pneumonias, New York J. Med. **52**:2005-2009 (Aug. 15) 1952.

3. Footnote 1*b*, *c*, *e*, and *f*.

4. Footnote 1*a*, *d*, and *f*.

those with erythromycin. On the other hand, the most impressive good result occurred with the use of carbomycin (Table 4) and both deaths were in the erythromycin group. Consequently, no fair comparison is possible, and none is made.

Before acceptance or rejection of a new antimicrobic agent as effective therapy for pneumococcal pneumonia, generally a large number of valid observations must be recorded which would indicate that its effect over a long period of time is as good as or better than the effect of a predecessor agent and that it is no more harmful to the human patient. In this sense the efficacy of penicillin, aureomycin, oxytetracycline, and chloramphenicol in the treatment of pneumococcal pneumonia has been well described.[5] Each appreciably reduces mortality and complications when compared with all previous drugs, none is toxic, and each has, therefore and rightly, been accepted as a drug of choice in the treatment of this one acute infection. Furthermore, each has achieved this therapeutic placing by being consistently good, regardless of the observer recording the result, or regimens used (within reason), or the degree of severity, or of the type of pneumonia being treated. It is, therefore, on the surface, unfair to judge any new drug with as few observations as are recorded here. On the other hand, these observations upon erythromycin and carbomycin have been made carefully and the judgment has been offered solely on the basis of the consistency of the early results. A complete failure rate of 25% in the case of erythromycin and 37.5% with carbomycin, slow resolution in 33 and 12.5% of the patients, respectively; bacteriological failure in 33 and 50% of the two groups, and satisfactory responses in less than one-half of the series are figures which can not be ignored. From these results, therefore, it does seem proper to draw early conclusions about the efficacy of erythromycin and carbomycin in the treatment of pneumococcal pneumonia—namely, that they are not agents of choice in the disease.

SUMMARY

Twelve patients with proved pneumococcal pneumonia were treated with an average of 1.5 gm. of erythromycin daily. The infection as a whole in the series was serious but not exceptionally severe when compared with previous experiences with pneumonia. Five of the 12 patients responded satisfactorily, and the pneumonia in each cleared promptly. The pneumonia in four others resolved slowly, but each eventually had complete clearing. Three of the 12 patients (25%) failed to respond satisfactorily; two developed empyema four to six days after treatment, and the infection in the third had not been controlled either clinically or bacteriologically after 96 hours of treatment. Two of the three died, one after 8 days, from empyema and lung abscess, and the other after 20 days, from a septic embolus to the superior mesenteric artery.

Eight patients were treated with carbomycin (Magnamycin) with an average daily dose of 1.6 gm. The age of the patients in this series averaged 62 years, and four of the eight had bacteremia. Four of the eight patients responded satisfactorily, and the pneumonia in a fifth patient cleared after six weeks. There were three clear-cut treatment failures (37.5%), bacteriologically and clinically, but no patient died.

Despite the fewness of the observations, it is concluded that erythromycin and carbomycin are not drugs of choice in the therapy of pneumococcal pneumonia.

5. Footnote 2*a*, *b*, *c*, and *d*.

RATE OF BLOOD REGENERATION AFTER BLOOD LOSS

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THE PHLEBOTOMY of the healthy donor is the simplest approach to the study of blood regeneration, since there is a controlled, known amount of blood loss and no impairment of hemopoiesis from disease. However, the measurement of blood regeneration after a single phlebotomy of 500 ml. is difficult because of the small change in red cell values, and this change is easily obscured by physiological fluctuations. Estimates of recovery time range from a few days [1] to several months.[2] Marked individual variation is found within any one group of donors; for example, Fowler and Barer [2b] noted recovery times of from 21 to 98 days among 63 subjects. In the present study repeated phlebotomies of donors have made it possible to establish a pattern of response, which can be applied to blood loss in general, be it of small or large amount.

METHODS

Normal subjects and patients with increased iron stores, between 20 and 40 years of age, were repeatedly phlebotomized in 500 ml. amounts. The specific conditions of the various studies are mentioned under Results. The subjects ate their usual diet, estimated to contain between 10 and 20 mg. of iron per day. Iron supplements, when given, consisted of 0.6 to 2.8 gm. of ferrous sulfate daily, taken immediately after meals, or saccharated oxide of iron [3] injected intravenously. Hematocrit readings and hemoglobin and serum iron determinations were performed before each phlebotomy.

Hemoglobin was measured as oxyhemoglobin on the Evelyn colorimeter. Hematocrit determination was performed by centrifugation at 3,000 rpm (radius 6 in. [15 cm.]) for one hour. Red blood cell counts were done in duplicate. Serum iron was determined by the method of Kitzes and his associates.[4] Ashby survival studies were performed according to a modification of the method

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1. (*a*) Jones, H. W.; Widing, H., and Nelson, L.: Blood Donors: Study of Effects in Donors of Repeated Blood Losses, J. A. M. A. **96**:1297, 1931. (*b*) Martin, J. W., and Myers, J. T.: The Effect of Blood Transfusion on Donors, J. Lab. & Clin. Med. **20**:593, 1935.

2. (*a*) Snapper, I.; Liu, S. H.; Chung, H. L., and Yu, T. F.: Anemia from Blood Donation, Chinese M. J. **56**:403, 1939. (*b*) Fowler, W. M., and Barer, A. P.: Rate of Hemoglobin Regeneration in Blood Donors, J. A. M. A. **118**:421, 1942.

3. Feojectin was supplied by Smith, Kline & French Laboratories, Philadelphia.

4. Kitzes, G.; Elvehjem, C. A., and Schuette, H. A.: The Determination of Blood Plasma Iron, J. Biol. Chem. **155**:653, 1944.

of Young and his associates.[5] Evans blue (T1824) determinations of blood volumes were made by the method of Gibson and Evans,[6] with a correction factor in the red cell mass of 0.85.[7] Plasma proteins were determined by salt precipitation and Kjeldahl digestion.[8]

Since no significant change in total blood volume was produced by bleeding after the plasma volume had reequilibrated, the change in hematocrit value was taken to represent a reliable index of the red cell deficit produced.

The rate of hemopoiesis was calculated in the following manner[9]:

1. Physiological hemopoiesis = 1% of the circulating red cell mass per day, or 7% per week. This is the normal red cell turnover.

2. Extra red cell regeneration each week = milliliters of red cells removed — milliliters of red cell deficit.

3. Hemopoiesis during a week of phlebotomy = extra red cell regeneration + normal red cell turnover.

When the mean age of donor cells is made younger by repeated phlebotomies, the turnover of the red cell mass should be decreased. Appropriate allowance is made for this by calculating the weekly production of new cells and assuming their life span to be 120 days. More detailed explanation of these calculations may be found in a previous publication.[9]

RESULTS

Plasma Protein Regeneration Following Phlebotomy.—The replacement of plasma protein was complete within a week in all subjects who were bled, even in those subjects losing up to 1,000 ml. of whole blood weekly. This applied both to the concentration and to the total amount of circulating plasma protein. To demonstrate the capacity for plasma protein regeneration, one subject was repeatedly phlebotomized with replacement of red cells over a period of six hours. A total of 1,000 ml. of plasma was thus removed without altering the red cell mass. The deficit was largely replaced within one week (Chart 1).

Red Cell Regeneration Without Supplemental Iron.—In four normal subjects 500 ml. phlebotomies were performed weekly for seven weeks. Progressive anemia developed, with a fall in hematocrit level to below 35% (Chart 2).

Two subjects with normal hematological values had a history of donating blood on several occasions and were suspected of having limited iron stores. They were bled 500 ml. weekly for five weeks. There was little evidence of blood regeneration, and the anemia was severe (Chart 2).

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5. Young, L. E.; Platzer, R. F., and Rafferty, J. A.: Differential Agglutination of Human Erythrocytes, J. Lab. & Clin. Med. **32**:489, 1947.

6. Gibson, J. G., II, and Evans, W. A., Jr.: Clinical Studies of Blood Volume: I. Clinical Application of a Method Employing the Azo Dye "Evans Blue" and the Spectrophotometer, J. Clin. Invest. **16**:301, 1937.

7. Gibson, J. G., II; Weiss, S.; Evans, R. D.; Peacock, W. C.; Irvine, J. W., Jr.; Good, W. M., and Kip, A. F.: The Measurement of the Circulating Red Cell Volume by Means of Two Radioactive Isotopes of Iron, J. Clin. Invest. **25**:616, 1946.

8. Fremont-Smith, K.; Volwiler, W., and Wood, P. A.: Serum Acetylcholinesterase: Its Close Correlation with Serum Albumin and Its Limited Usefulness as a Test of Liver Function, J. Lab. & Clin. Med. **40**:692, 1952. Serum protein determinations were performed through the cooperation of Dr. Wade Volwiler.

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Four patients with excessive iron stores associated with other clinical manifestations of hemochromatosis were bled weekly for seven weeks. They showed active regeneration of blood, with hematocrit levels maintained at approximately 40% (Chart 2).

Red Cell Regeneration with Supplemental Iron.—In one study bleedings were performed every two weeks for a period of eight months. The subjects consisted of one normal male, two normal menstruating females, and one woman with menorrhagia and mild iron deficiency. The first three were placed on a regimen

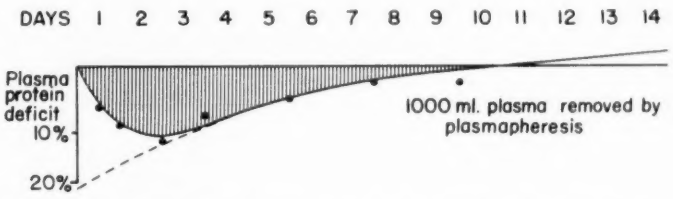

Chart 1.—Plasmapheresis was performed in a normal subject, with removal of 1,000 ml. plasma but with no change in the red cell mass, over a period of six hours. The shaded area represents the decrease in concentration of circulating plasma proteins. The first dot below Day 1 represents the determination immediately after plasmapheresis. The dotted line represents the anticipated fall in concentration if blood volume remained constant. Decreased plasma volume and perhaps some immediate mobilization of plasma protein account for the discrepancy.

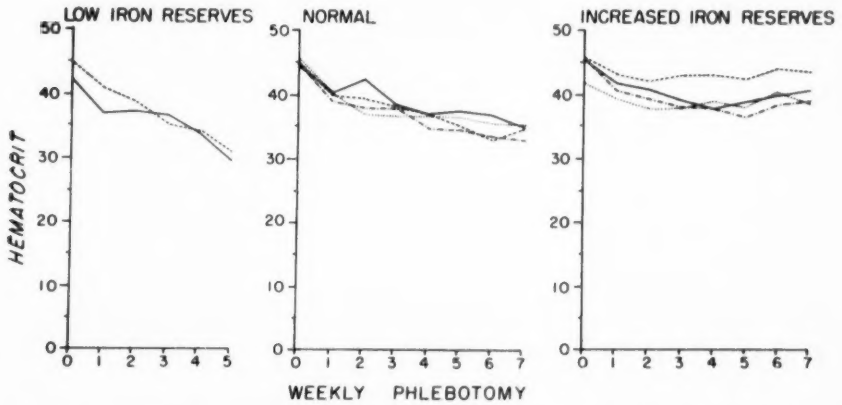

Chart 2.—Phlebotomy without supplemental iron. Subjects were bled 500 ml. weekly. All subjects had essentially normal blood values at the beginning of the study. Two subjects (low iron reserves) had given several transfusions in previous years, four subjects (normal) had no history of excessive iron losses, and four subjects (increased iron reserves) had hemochromatosis. It is evident that the iron stores of the individual determines the degree of anemia produced by bleeding, as shown in the fall of the hematocrit level.

of 1.0 gm. of ferrous sulfate daily through the experimental period. The fourth was given saccharated oxide of iron intravenously in amounts equivalent to the iron removed. The hematocrit level in this group initially averaged 42.5% and had fallen to 39.5% by the end of the experiment (Chart 3).

Two male donors (not portrayed graphically) were bled weekly for seven weeks, during which time they took 0.6 and 1.2 gm. of ferrous sulfate daily. Their hematocrit levels appeared to stabilize at 39% by the seventh week.

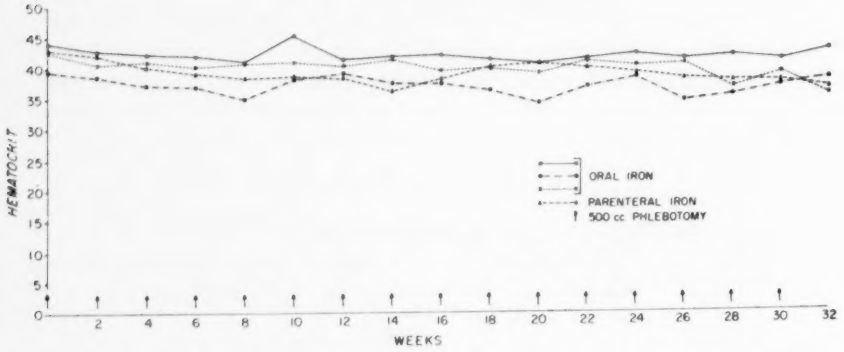

Chart 3.—The effect of repeated phlebotomies on the hematocrit level in subjects taking supplemental iron salts. One male and two females ingested 1.0 gm. ferrous sulfate daily. One female, who had been mildly iron deficient for several years, was given intravenous iron replacement after each phlebotomy. Bleedings were continued every two weeks for eight months. The average hematocrit level dropped from 42.5 to 39.5% during the study. No symptoms were produced by the bleedings.

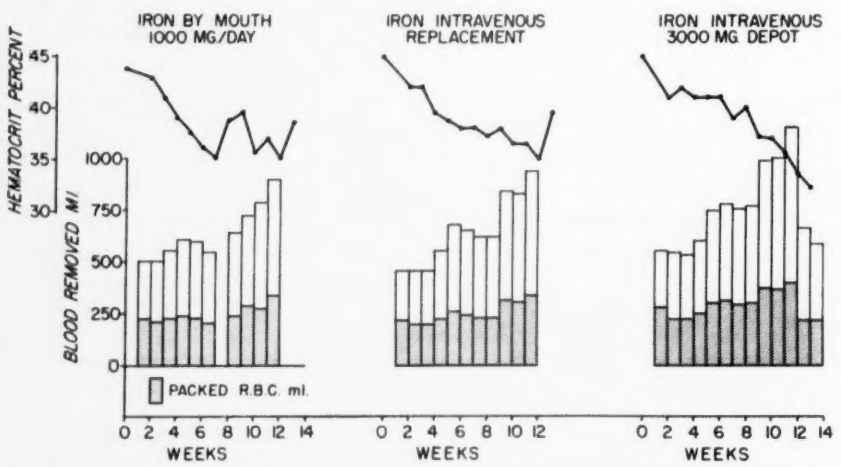

Chart 4.—Large bleedings with iron supplementation. The amount of blood and of red cells removed each week and the associated change in hematocrit level in 3 subjects are shown. It was possible to remove from 500 to 1,000 ml. of blood a week over several weeks in these subjects given iron orally or parenterally without lowering their hematocrit levels below 35% or producing severe symptoms.

Three male subjects were bled repeatedly over a period of 12 weeks amounts of blood up to 1,000 ml. weekly. One subject took 1 gm. of iron by mouth daily (2.8 gm. $FeSO_4$), another was given injections of saccharated iron oxide to replace

iron lost in each phlebotomy, and the third was given 3,000 mg. of iron intravenously before the phlebotomies were begun. Their hematocrit levels and the amount of blood removed weekly are illustrated in Chart 4.

Rates of Blood Regeneration.—The amount of blood produced by the donors is a composite of (*a*) replacement of dying erythrocytes and (*b*) replacement of the red cells removed by phlebotomy. In a mixed population of red cells a constant breakdown and synthesis of about 1% per day occurs. However, repeated phlebotomies replace a mixed cell population with predominantly young cells. This would theoretically require little replacement during the first 100 days. In Chart 5 is shown evidence that such a skewing of cell population occurs and that this assumption in the calculation of cell breakdown is valid.

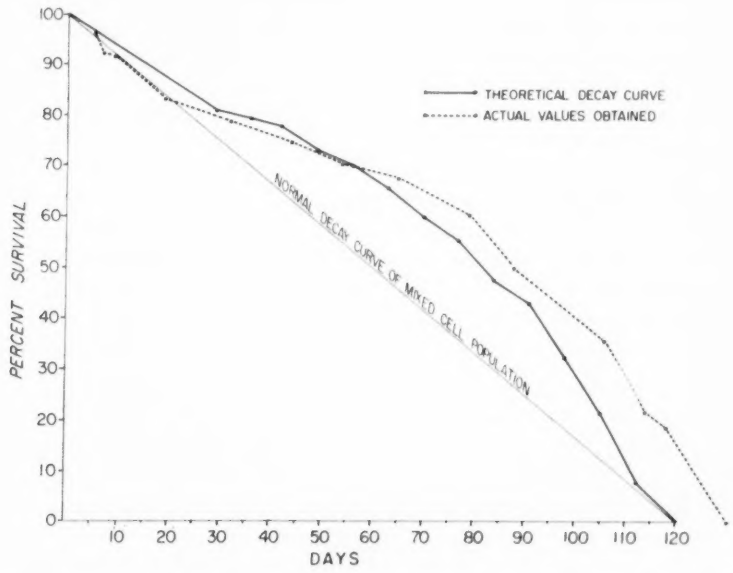

Chart 5.—Survival of a skewed population of erythrocytes. This blood was drawn from the third subject illustrated in Chart 4, who had been bled 9,655 ml. over 14 weeks. Data obtained during the phlebotomy period allowed the calculation of the age of this blood and, assuming a life span of 120 days, the theoretical decay curve of the red blood cells. The actual figures, obtained by the Ashby differential agglutination technique, appear to be close enough to make subsequent calculations of hemopoietic rates valid.

The rate of blood production following blood loss is shown in Chart 6. Normal subjects bled 500 ml. weekly increased their rate of hemopoiesis to one and two-thirds of normal through the fourth or fifth week; hemopoiesis then fell to the prephlebotomy level, despite the presence of anemia (hematocrit level 35%). Iron-depleted subjects showed a very temporary response to less than one and one-half times normal during the second and third week and were subnormal thereafter. Patients with excessive iron stores maintained an active hemopoiesis of one and one-half to two times normal, with minimal anemia. When supplementary iron was given, hemopoiesis was sustained at one and one-half to two times normal in

individuals bled weekly or every two weeks. Subjects bled 500 to 1,000 ml. weekly were able to increase blood production to slightly over twice normal, provided iron was administered.

Symptoms Produced by Bleeding.—In one subject mild syncopal reactions were observed immediately after the first few phlebotomies. In a second subject symptoms associated with a decreased blood volume, dizziness, sweating, and weakness, were observed in the first 24 hours. In both instances these symptoms disappeared as phlebotomies were continued, and they had no relation to anemia.

With a hematocrit of 40% or above there were no symptoms. Between 35 and 40%, slight symptoms were occasionally reported. These were in no sense inca-

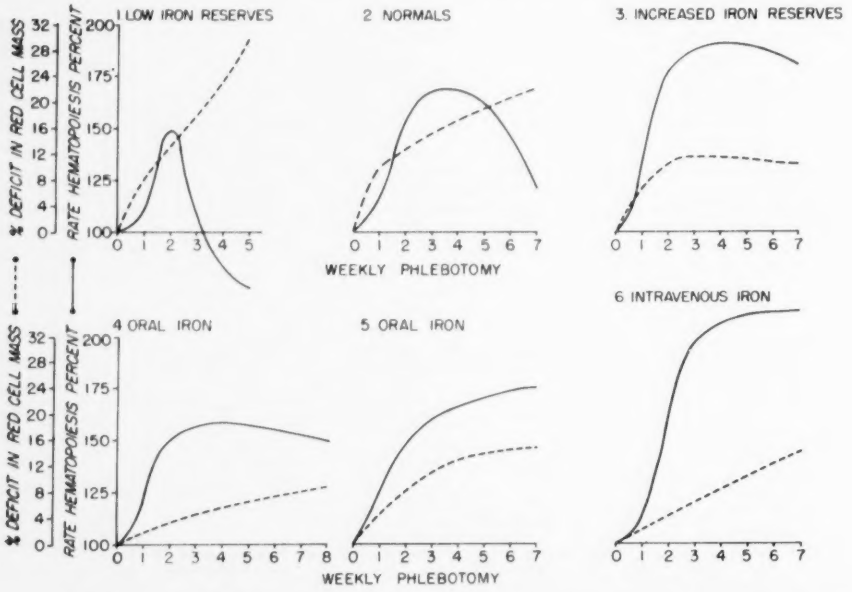

Chart 6.—Rates of hemopoiesis and deficits in cell mass are depicted percentagewise, the former in comparison to the normal of 100%. Red cell regeneration is poorly maintained and the anemia severe in individuals bled 500 ml. weekly and not receiving supplemental iron (Graphs 1 and 2). Oral iron was effective in sustaining increased hemopoiesis in the face of bimonthly (Graph 4) or weekly (Graph 5) phlebotomies of 500 to 1,000 ml. The anemia was less severe. Weekly bleedings of 500 to 1,000 ml. in subjects with increased iron stores (Graphs 3 and 6) yielded the greatest increment in blood production and the least degree of anemia.

pacitating and did not interfere with strenuous activity. Below 35% symptoms were definite, including mild fatigue, palpitation, dyspnea and excess sweating with exercise, and the necessity for an increased amount of sleep.

COMMENT

Plasma Regeneration.—Large amounts of plasma protein and hemoglobin must be synthesized to replace the deficit produced by phlebotomy. Plasma protein is rapidly regenerated and repeated phlebotomies have not produced significant depletion in normal subjects; 1,000 ml. of plasma removed over a period of six

hours was largely replaced in one week (Chart 1). Other reports [10] also indicate that weekly phlebotomies do not produce significant plasma protein deficits. This would be anticipated from studies of turnover rate of plasma proteins,[11] indicating a normal turnover rate of plasma proteins 5 to 10 times that of hemoglobin. Reserve stores of mobilizable protein have also been demonstrated in animals [12] and man.[13] It is concluded that replacement of plasma protein following phlebotomy is of no concern. It is to be emphasized that this conclusion pertains only to normal subjects on normal diets. Two instances of protein depletion have been observed by us following phlebotomies in chronic alcoholics with cirrhosis, and instances have been reported in malournished subjects.[14]

Hemoglobin Regeneration.—The essential factors in erythropoiesis are the stimulus for blood production, the functional capacity of the marrow, and the available supplies of building materials.

The intensity of stimulus for erythropoiesis may be assumed to be inversely proportional to the hematocrit level. This has been illustrated by studies of bleeding in dogs [15] and by the bone-marrow-inhibiting effect of transfusions.[16] It is also evident in these studies that, while an average time of 40 days is required to regenerate 500 ml. of blood,[2b] 3,500 ml. of blood was replaced in normal subjects in 100 to 120 days.

The demand placed on the marrow for regeneration of a 500 ml. phlebotomy in one week is a hemopoietic rate of one and one-half times normal. Since in hemolytic anemias various measurements of hemopoiesis indicate rates of blood production of 5 to 10 times normal,[17] the demands imposed in this study on the bone marrow would be expected to lie well within marrow capacity. The difference between these conditions is that hemolytic anemias do not result in a loss of the products of red cell

10. Griffols-Lucas, J. A.: Foreign Letters, J. A. M. A. **147**:989, 1951. Co Tui; Bartter, F. C.; Wright, A. M., and Holt, R. B.: Red Cell Reinfusion and the Frequency of Plasma Donations, J. A. M. A. **124**:332, 1944.

11. London, I. M.: Plasma Proteins, edited by J. B. Youmans, Springfield, Ill., Charles C Thomas, Publisher, 1950, Vol. 2, p. 72. Sterling, K.: The Turnover Rate of Serum Albumin in Man as Measured by I-131 Tagged Albumin, J. Clin. Invest. **30**:1228, 1951. Yuile, C. L.; Lamson, B. G.; Anderson, L. B., Jr., and Whipple, G. H.: Excretion and Tissue Distribution of C14 Following Intravenous Injection of Labeled Plasma Protein, Fed. Proc. **9**:350, 1950. Volwiler, W.; Fremont-Smith, K., and MacMartin, M. P.: Turnover Rates of Serum Proteins in Cirrhotic Man, J. Clin. Invest. **31**:668, 1952.

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14. Bateman, J. C.: Treatment of Chronic Blood Donor Anemia, Ann. Int. Med. **34**:393, 1951.

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17. Coleman, D. H., and Finch, C. A.: Unpublished data.

catabolism from the body. It would not be unexpected therefore that deficiency in a building material might be the limiting factor in hemopoiesis following blood loss. This deficiency is in iron.

In evaluating response to phlebotomy the first consideration is the iron-depleted subject. It has previously been shown that 80 to 90 days are required in depleted patients with polycythemia vera to replace the erythrocytes removed in 500 ml. of blood.[9] If blood loss from menstruation or other causes is superimposed on exhausted iron stores, even longer time would be required.

While the normal subject has a much greater capacity to regenerate blood, this capacity is proportional to his iron reserve. Persons with normal hematological findings may have depleted stores, normal stores, of 1 to 1.5 gm., or stores of much greater size.[18] An approximation of the size of these stores can be made by sternal marrow examination.[19]

If iron deficiency is obviated by administration of iron, the studies reported provide a format of the rates of hemopoiesis and the severity of anemia with different quantities of blood-letting. In male subjects bled 500 to 1,000 ml. weekly a packed red cell mass of about 35% (deficit of 10%) and a hemopoietic rate of twice normal were found. Subjects bled 500 ml. weekly demonstrated a packed red cell mass of 37.5% (deficit of 7.5%) and hemopoiesis one and one-half to two times normal. In subjects bled 500 ml. every two weeks a packed red cell mass of 42% (deficit of 3%) and a hemopoietic rate of one and one-half times normal were found. The values for packed red cell mass would be 3% lower in women. Definite symptoms of anemia were found with depression of the hematocrit level of 10%, mild symptoms between 5 and 10%, and no symptoms when the deficit was less than 5%.

It is apparent that supplemental iron therapy must be given to insure rapid regeneration of blood after phlebotomy. The data of Barer and Fowler and of Santy [20] indicate that complete replacement will then occur within one month. Our data indicate that if iron is taken continuously 500 ml. phlebotomies may be performed as often as every two weeks for many months without the development of sufficient anemia to produce symptoms. Even at weekly intervals phlebotomies will be tolerated with only moderate anemia and borderline symptoms.

In most of the reports of regeneration after phlebotomy it is emphasized that females may be slow in replacement of blood.[21] In view of the smaller iron stores and the frequent mild iron deficiency anemia in the female [20a] this would be expected. Menstruation is important not so much in terms of the increased blood production required but in terms of the iron depletion which it effects. It is in the female blood donor that routine iron therapy would appear to be most useful.

18. Haskins, D.; Stevens, A. R., Jr.; Finch, S., and Finch, C. A.: Iron Metabolism: Iron Stores in Man as Measured by Phlebotomy, J. Clin. Invest. **31**:543, 1952.

19. Stevens, A. R., Jr.; Coleman, D. H., and Finch, C. A.: Iron Metabolism: Clinical Evaluation of Iron Stores, Ann. Int. Med. **38**:199, 1953.

20. (*a*) Barer, A. P., and Fowler, W. M.: The Effect of Iron on the Hemoglobin Regeneration in Blood Donors, Am. J. M. Sc. **205**:9, 1943. (*b*) Santy, A. C.: Response of Blood Donors to Iron, ibid. **201**:790, 1941.

21. Giffin, H. Z., and Haines, S. F.: A Review of a Group of Professional Donors, J. A. M. A. **81**:532, 1923. Hervey, G. W.; McIntire, R. T., and Watson, V.: Low Hemoglobin Levels in Women as Revealed by Blood Donor Records, ibid. **149**:1127, 1952. Jones and others.[1a] Fowler and Barer.[2b]

SUMMARY

The rate of blood regeneration following blood loss has been quantitatively determined in man. Blood production is proportional to the amount of available iron, whether derived from iron stores or from iron ingestion. There may be a depletion of body iron stores despite normal peripheral blood values. In such instances, bleeding results in little or no increase in blood production. On the other hand, adequate available iron permits an acceleration of hemopoiesis to two to three times the normal rate. The variability from two or three weeks to three or four months in recovery from a 500 ml. phlebotomy may be explained on the basis of variable iron stores. When supplementary iron is given, phlebotomies may be performed every two weeks without the production of significant anemia. Since the peripheral blood values give no indication of iron stores, it seems advisable to provide supplemental iron therapy to all blood donors. If this is done, the interval between blood donations need be no more than two to three weeks.

HEMOPERICARDIUM ASSOCIATED WITH ANTICOAGULANT THERAPY

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THE INCREASED use of anticoagulant therapy in the prevention of thromboembolic phenomena has led to frequent reports of numerous hemorrhagic manifestations. It is the purpose of this paper to review the literature and report three cases of hemopericardium, a serious complication associated with anticoagulant therapy. The early recognition of this complication and the prompt institution of therapy are mandatory for survival.

Hammarsten,[1] in 1949, first described hemopericardium without rupture of the heart following bishydroxycoumarin therapy for myocardial infarction. He reported a case of a 58-year-old man with an anterior myocardial infarction, in which bishydroxycoumarin therapy was instituted immediately after the diagnosis was established. The usual doses of bishydroxycoumarin were given, but the percentage of prothrombin concentration on frequent occasions was extremely low and on one occasion the prothrombin time was as long as 132 seconds. On the 24th hospital day the patient's condition deteriorated, with a drop of blood pressure from a level of 106/70 to 40/0. The liver was not palpable, but the neck veins were reported markedly distended, and the patient died shortly thereafter. At autopsy the pericardial cavity contained 800 cc. of dark red blood, although a very careful and extensive search failed to reveal any small rupture of the ventricular wall or blood vessels of the heart. Hammarsten suggested that the bishydroxycoumarin was of etiological significance in the production of the hemopericardium.

Nichol[2] reported five cases of hemopericardium associated with anticoagulant administration. However, in reviewing the article, we can find substantiating evidence in only one case that bishydroxycoumarin could have been the sole etiologic agent. The case is that of a 42-year-old man with an electrocardiogram characteristic

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Pathologist, Wilkes-Barre General Hospital (Dr. Rodriguez).

1. Hammarsten, J. F.: Hemopericardium Without Rupture of the Heart Following Dicumarol Therapy for Myocardial Infarction, Minnesota Med. **32**:1003, 1949.

2. Nichol, E. S.: The Risk of Hemorrhage in Anticoagulant Therapy, Ann. West. Med. & Surg. **4**:71, 1950.

of an acute posterior myocardial infarction. Bishydroxycoumarin therapy was started immediately, and a rapid prolongation in prothrombin time followed, thereafter requiring small doses of bishydroxycoumarin for maintenance. On the 15th hospital day chest pain recurred and was followed the next day by a fall in blood pressure. The patient's condition declined, and he died the same day. Autopsy revealed a hemopericardium of 600 cc. of unclotted blood, without evidence of perforation or rupture of the cardiac musculature or any of the vessels. It was felt by this observer that the anticoagulant therapy played a role in the production of the hemopericardium and that the latter, by causing tamponade, was a prominent factor in the cause of death.

Leedham and Orbison [3] reported a case of traumatic pericarditis and probable contusion of the heart in a 22-year-old man. The patient was given bishydroxycoumarin therapy, with minimum prothrombin activity of 24%. On the 10th day there was a sudden onset of substernal pain. The blood pressure dropped from 130/80 to 70/40, the cervical veins were distended, the pulse was paradoxic in type, and a friction rub was heard at the left sternal border. The signs were such that despite the prothrombin reports the possibility of a hemorrhagic pericardial effusion was considered, and therapy, which consisted of vitamin K and blood transfusions, was instituted. A pericardial paracentesis was done, and 380 cc. of dark nonclotting blood was removed. The patient made a favorable and uneventful recovery. The role of bishydroxycoumarin as the etiological agent in the production of hemopericardium in this case is not clear, but it was felt by the author that bishydroxycoumarin therapy enhanced bleeding from a previously contused myocardium.

Goldstein and Wolff [4] report five cases, two of which are reported in the addendum to their article. The first patient was a 42-year-old white man with a diagnosis of acute posterior myocardial infarction, who was treated with bishydroxycoumarin. Prothrombin activity varied between 96 and 23%. The blood pressure for the first 15 days was 110/70. On the 15th day rales in both lung bases and slight cyanosis developed. Anterior chest pain recurred, and with this the blood pressure dropped to 90/70. On the following day there was cervical vein distention and profound peripheral vascular collapse and the patient died. Autopsy revealed 600 cc. of bloody fluid in the pericardium. There was no evidence of myocardial perforation or blood vessel rupture. The second patient was a 66-year-old white woman with a posterior myocardial infarction with complete auriculoventricular block. The patient was treated with bishydroxycoumarin, the prothrombin activity ranging between 55 and 2%. On the 11th day severe paraumbilical pain developed, which was followed by peripheral vascular collapse; the blood pressure was unobtainable. The patient died shortly thereafter. Autopsy revealed marked pericardial adhesions, and the pericardium contained 50 to 75 cc. of bloody fluid. There was no rupture of the myocardium or blood vessel perforation. The third case occurred in a 48-year-old white man with an extensive acute anterior myocardial infarction. Bishydroxycoumarin therapy was instituted, and the prothrombin time was maintained between

3. Leedham, C. L., and Orbison, J. A.: Cardiac Tamponade Associated with the Administration of Dicumarol, Circulation **1**:1065, 1950.

4. Goldstein, R., and Wolff, L.: Hemorrhagic Pericarditis in Acute Myocardial Infarction Treated with Bishydroxycoumarin, J. A. M. A. **146**:616, 1951.

20 and 30 seconds. On the 13th hospital day there was a recurrence of chest pain, cyanosis, weakness, and profuse diaphoresis, with no change in blood pressure but a rise in the heart rate, and the patient's condition appeared to be deteriorating. Repeat electrocardiogram showed no evidence of fresh infarction. A chest film revealed an increase in heart size consistent with a pericardial effusion. The bishydroxycoumarin was discontinued and therapy with intravenous vitamin K begun. Thereafter the clinical course was uneventful, and the patient was discharged from the hospital on the 42d day of her illness.

Russek and Zohman [5] received 228 replies from questionnaires sent to medical specialists in various medical centers. Twenty cases of death presumed to have been due to hemorrhagic pericarditis in patients receiving anticoagulant therapy were reported. We feel that positive proof of the pericarditis attributable solely to the therapy is lacking.

REPORT OF CASES

CASE 1.—C. C., a 60-year-old white man, was admitted to the Binghamton City Hospital (service of Drs. V. Maddi and G. Hamilton) on Aug. 6, 1952, with the chief complaints of severe substernal pain, weakness, and marked perspiration of a few hours' duration. On admission to the hospital the patient appeared acutely ill, with moderate dyspnea and pallor. The temperature was 97.4 F., pulse rate 72, and blood pressure 190/110; heart sounds were distant but audible; no murmurs or friction rubs were heard. Results of admission studies were as follows: the red blood cell count was 3,800,000, hemoglobin 74%, and white blood cell count 9,050, with a relatively normal differential count. The sedimentation rate was 17 mm. per hour. The urine was essentially normal. An electrocardiogram revealed typical changes compatible with recent posterior myocardial infarction with significant Q waves in Leads II, III, and aV_F; reciprocal RST changes in Leads I and III, and the same changes in Leads aV_L and aV_F. The patient was treated symptomatically with morphine and oxygen, and it was not until the fifth hospital day that anticoagulant therapy with bishydroxycoumarin was begun, in the usual doses. The patient's progress seemed to be satisfactory in the following days except for low-grade temperature elevations. The prothrombin activity percentage was maintained in a therapeutic range between 17 and 30%, never reaching any extremely low level. On the 15th hospital day the patient again experienced substernal and epigastric pain and again appeared acutely ill. The blood pressure dropped to 120/80, and the liver became palpable two to three fingerbreadths below the costal margin and was extremely tender. A repeat electrocardiogram was compatible with a healing posterior myocardial infarction without evidence of new injury. The red blood cell count at that time was 3,290,000 cells per cubic millimeter, and the hemoglobin was 56%. Roentgenograms of the chest (Fig. 1) revealed tremendous increase in heart size and satisfied the requirements for the diagnosis of pericardial effusion. The diagnosis of hemopericardium was immediately suspected, and bishydroxycoumarin therapy was stopped; therapy with intravenous vitamin K was begun along with whole blood transfusion. Since the patient never exhibited any signs of severe cardiac tamponade, pericardial paracentesis was not done. The patient made an uneventful recovery and was discharged on the 44th hospital day.

CASE 2.—K. M., a 59-year-old white woman, was admitted to the Binghamton City Hospital (service of Dr. N. Brown) on Nov. 25, 1952, with the chief complaint of sudden onset of severe substernal pain of two hours' duration. Significant past history was that of hypertension. On admission to the hospital the patient appeared acutely ill, and she was extremely apprehensive. The pulse rate was 100 per minute, and the blood pressure was 150/90; the heart sounds were distant and feeble. The red blood cell count was 4,280,000 cells per cubic millimeter, hemoglobin 84%, and white blood cell count 22,500 per cubic millimeter, with a differential shift to the left.

5. Russek, H. I., and Zohman, B. L.: Anticoagulant Therapy in Acute Myocardial Infarction: A Survey of Specialists' Opinions Concerning Indications, Results and Dangers, Am. J. M. Sc. **225**:8, 1953.

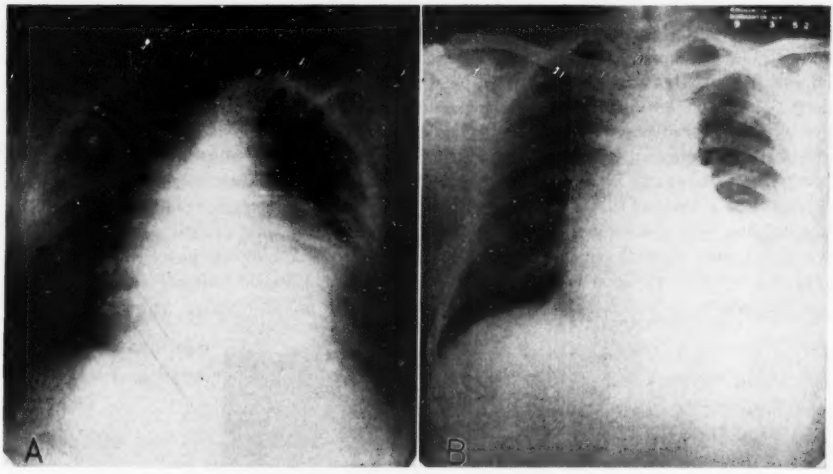

Fig. 1 (Case 1).—*A*, chest x-ray taken 15 days after admission, showing marked pericardial effusion. *B*, follow-up x-ray taken two weeks after that in Figure 1, showing diminution in the transverse diameter of the heart.

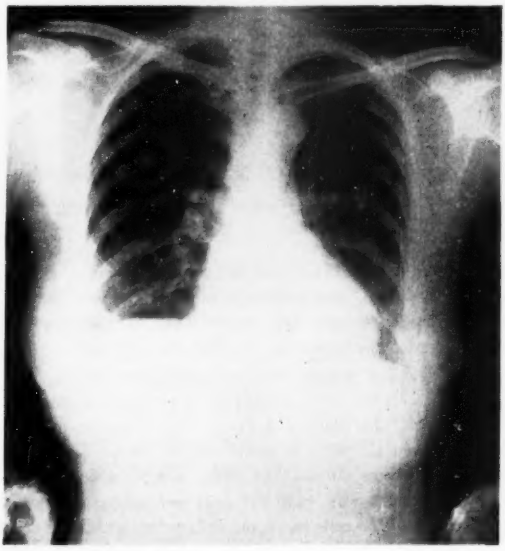

Fig. 2 (Case 2).—Chest x-ray taken on admission, showing mild cardiac enlargement and mild congestive changes in the lung parenchyma.

The urinalysis showed no abnormalities. Initial roentgenogram of the chest (Fig. 2) revealed cardiac enlargement in the transverse diameter and mild congestive changes in the lung parenchyma. An electrocardiogram was compatible with an acute extensive anterior myocardial infarction consisting of marked reciprocal RST changes in the limb leads and large Q waves and RST-segment elevations in all the precordial leads. With the diagnosis of myocardial infarction established, anticoagulant therapy with bishydroxycoumarin was begun in the usual doses. In the following days the patient continued to complain of persistent substernal pain despite fairly large doses of narcotics. The patient appeared to be sensitive to small doses of bishydroxycoumarin, so that the prothrombin percentage activity fell to low levels, the lowest being 12% of normal. On the ninth hospital day gross hematuria was noted but anticoagulant therapy was continued cautiously without recurrence of urinary tract bleeding. On the 23rd hospital day, with the patient still complaining of precordial pain, unusual pallor of the skin was noted, with cervical vein distention and hepatomegaly. A complete blood count was done, revealing evidence of blood loss, with a red cell count of 2,790,000 cells per cubic millimeter, and hemoglobin 61%. A roentgenogram of the chest (Fig. 3) revealed marked increase in

Fig. 3 (Case 2).—Chest x-ray 23 days after admission, showing evidence of pericardial effusion and left hydrothorax.

heart size in comparison with the initial film and a large pleural effusion. The diagnosis of hemopericardium was suspected, and anticoagulant therapy was immediately discontinued. Cardiac decompensation developed and the patient had a somewhat stormy course but subsequently recovered and was discharged on the 70th hospital day.

Case 3.—S. S., a 53-year-old white man, was admitted to the Wilkes-Barre General Hospital on Sept. 10, 1952, with the chief complaint of severe precordial pain of a few hours' duration radiating to the arms, shoulders, and neck. On admission to the hospital the patient appeared seriously and acutely ill, with a pulse rate of 70 per minute and blood pressure of 114/80. The heart sounds were audible but weak, and no murmurs or friction rubs were heard. The red blood cell count was 4,290,000 cells per cubic millimeter, hemoglobin 82%, and the white blood cell count 13,150 cells per cubic millimeter, with a differential shift to the left. An electrocardiogram revealed typical changes of acute posterior myocardial infarction with marked RST reciprocal changes in Leads I and III and the same RST elevations and depressions in Leads aV_L and aV_F, along with marked RST depressions in Leads V_2 through V_6. With the diagnosis of myocardial infarction established, anticoagulant therapy was begun with ethyl biscoumacetate (Tromexan) in the usual doses. The patient's progress was satisfactory, with the prothrombin percentage activity well within the therapeutic range, of 17 to 32%

of normal. On the 16th hospital day the patient experienced recurrence of severe chest pain and again became acutely ill, as evidenced by marked pallor, cervical vein distention, hepatomegaly, and severe hypotension, with a blood pressure of 70/0. In spite of the use of pressor drugs, the blood pressure could not be sustained, and the patient died three days later. At necropsy the pericardial sac was found to be distended, and on opening the pericardial cavity, there was found about 600 cc. of partly clotted blood. Careful inspection of the epicardial surface of the heart revealed a diffuse serosanguinous film attached to the posterior wall of the left ventricle over an area of recent infarction. Careful inspection of the area failed to reveal any evidence of perforation. The right coronary artery revealed a well-formed thrombus close to the ostium. Careful inspection of the coronary system failed to reveal any evidence of rupture, nor was there any perforation of the larger vessels. The liver was enlarged, weighing 2,700 gm., and was characterized by recent severe centrilobular necrosis with marked congestive changes.

COMMENT

In the three cases reported one of the earliest signs of hemopericardium is recurrence of cardiac pain. It is interesting to note that there is a similar pattern in the development of hemopericardium in these three cases: first, recurrence of precordial pain after a pain-free interval; second, relatively sudden onset of circulatory collapse, accompanied by a drop in blood pressure, hepatomegaly, and distended neck veins; third, sudden onset of unexplained anemia, as evidenced by laboratory data in two patients and extreme pallor in the third, fourth, roentgenographic evidence of pericardial effusion.

In all the cases reported in the literature, including the above three, recurrence of cardiac pain without electrocardiographic evidence of extension of the myocardial infarction is the predominant symptom, followed shortly by circulatory collapse. In some of the patients hepatomegaly and neck vein distention developed. Prior to this report there has been no mention in the literature of rapidly developing anemia, and we feel that this is an important corroborating finding in the diagnosis of hemopericardium. The roentgen examination of the heart can be of invaluable assistance in arriving at the diagnosis of hemopericardium, as revealed by our two cases, in which it was interpreted as consistent with this diagnosis.

The possible contributory factors in the production of hemopericardium associated with myocardial infarction in patients treated with anticoagulants are weakening of the myocardial fibers by the disease, with damage to the epicardial vessels, and the anticoagulant effect on the blood, thus aggravating the hemorrhage. The function of the liver in cases of myocardial infarction is partly impaired by the severe centrilobular necrosis which is nearly always proportional to the size of the infarcted area. We have observed that there is a poor prognosis for patients with myocardial infarction treated with an anticoagulant when the prothrombin activity drops sharply after small doses have been given.

We feel that alertness on the part of the physician, with anticipation and early recognition of this serious complication in patients receiving anticoagulants, particularly those suffering from recent myocardial infarction, will certainly lower the mortality, as evidenced by the four cases of survival in which it was recognized. Therapy should be directed to the discontinuance of the anticoagulants, transfusion of whole blood or plasma, use of vitamin K, and pericardial paracentesis when there are signs of cardiac tamponade.

SUMMARY

A review of the literature has been made of cases of hemopericardium associated with anticoagulant therapy, and three additional cases are reported, two associated with bishydroxycoumarin and one with ethyl biscoumacetate (Tromexan) therapy. This is the first reported case of hemopericardium associated with ethyl biscoumacetate.

The diagnosis of hemopericardium should be suspected in the presence of (*a*) recurrent chest pain without renewed electrocardiographic evidence of recent myocardial injury, (*b*) a prolonged and persistent or recurrence of a friction rub, (*c*) circulatory collapse accompanied by a drop in blood pressure, relatively sudden hepatomegaly, and distended neck veins, (*d*) sudden onset of unexplained anemia, and (*e*) roentgenographic evidence of pericardial effusion.

Early diagnosis of the complication of hemopericardium will reduce mortality.

Miss Marie Kerwin, medical librarian, gave assistance in securing data and material used in this article.

Progress in Internal Medicine

REVIEW OF THE 1952 HEMATOLOGY LITERATURE

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IT IS THE intention of this review to survey the pertinent 1952 hematology literature. For the sake of continuity, there is some overlapping into the preceding and succeeding years. Liberal use is made of other reviews, editorials, abstracts of proceedings of recent meetings, and the excellent summations of *Nutrition Reviews*.

The volume of available scientific literature has been progressively mounting. Although no specific figures are available in the field of hematology per se, the increase in the general scientific field may be indicated by the 10 to 12% yearly increase in chemistry publications since 1946. For this particular survey approximately 1,500 articles were reviewed and approximately 900 included. Although a comprehensive coverage of the literature has been attempted, our limitations have made certain oversights and omissions inevitable.

Different subjects demand different presentation of the material. For instance, at one extreme is the excellent objective reporting of progress in the study of erythrocyte maturation factor metabolism and macrocytic anemias, which allowed facile documentation. On the other hand, much of the available material on therapy of the leukemias contains considerable subjective reporting. In order to effect adequate continuity, our opinions are frequently expressed. The bulk of the remaining material lies between these two extremes.

Schematic diagrams have been compiled with the hope of facilitating review of the folic acid-nucleoprotein metabolism (Fig. 1), iron metabolism (Fig. 2), and diagnosis of the hemolytic syndromes (Fig. 3).

The only phase of coagulation included is that concerned with platelet influences.

SPECIAL TOPICS

TECHNIQUES

To prevent chance transmission of homologous serum jaundice, a heat-resistant plastic case containing stainless steel lancets has been devised for easy cleaning and

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sterilization of lancets.[1] A new technique facilitates sterile division of blood samples into small aliquots.[2] Types of nonwettable surfaces and their means of application have been evaluated.[3] A new machine for mixing cell suspensions is described.[4] The advantages offered by phase [5] and ultraviolet [6] microscopy have been applied to studies in hematology.

Good correlation has been obtained between direct cell counts and nephelometry (light reflection) or distant opacimetry (light absorption) cell-counting techniques, but not between direct cell counts and proximal opacimetry.[7] Use of an automatic microslide projector and a new staining procedure allows rapid preparation and examination of blood films.[8] A method for the observation of stained living blood cells by fluorochromizing them with acridine orange is reported.[9]

In red blood cell studies a most promising technique measures the radioactive iron "turnover" in a prescribed interval. It has proved valuable in studies of erythrocyte production in general [10] and of a large number of hematologic disturbances.[11]

The recent refinement and simplification of many techniques for more accurate measurement of the circulating red blood cell mass and plasma have resulted in marked advances in basic research and in clinical diagnosis and therapy.[12] An exam-

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12. (*a*) Wiseman, B. K.: Spurious Anemia, editorial, A. M. A. Arch. Int. Med. **90**:577, 1952. (*b*) Wilson, S. J., and Boyle, P.: Erroneous Anemia and Polycythemia: A Comparative Study of Peripheral Blood and Blood Volume, ibid. **90**:602, 1952. (*c*) Hahn, P. F.; Ross, J. F.; Bale, W. F., and Balfour, W. M.: Red Cell and Plasma Volumes (Circulating and Total) as Determined by Radio Iron and by Dye, J. Exper. Med. **75**:221, 1942. (*d*) Gibson,

(*Footnotes continued on next page*)

ple is the recognition of the prevalence of the "relative," "spurious," or "erroneous" anemias and polycythemias. This is discussed on pages 413 and 414.

Other techniques described for studies on erythrocytes include a hematocrit centrifuge,[13] a microhematocrit method requiring only 0.02 ml. of blood,[14] a single-tube screening test in conjunction with a photoelectric oxyhemoglobin method of hemoglobin estimation for rapid measurement of red cell fragility,[15] a method for staining vital granulation in granulocytes,[16] and a research method for enumeration of individual marrow elements.[17] A modified spectrophotometric method for the detection of blood stains is described for use in forensic medicine.[18] The inner structure of erythrocytes has been studied by means of the electron microscope.[19]

The development and refinement of a battery of techniques for more accurately diagnosing hemolytic anemia in the last few years are outlined and reviewed on page 408.

Special methods for the study of the hemoglobin in sicklemia and/or thalassemia are the hemoglobin alkali resistance test,[20] study of the electrophoretic mobility of hemoglobin,[21] and the use of rabbit antiserum which is specific against the erythrocytes of sickle cell anemia.[22]

J. G., II; Weiss, S.; Evans, R. D.; Peacock, W. C.; Irvine, J. W., Jr.; Good, W., and Kip, A. F.: Measurement of Circulating Red Cell Volume by Means of 2 Radioactive Isotopes of Iron, J. Clin. Invest. **25**:616, 1946. (*e*) Sterling, K., and Gray, S. J.: Determination of Circulating Red Cell Volume in Men by Radioactive Chromium, ibid. **29**:1614, 1950. (*f*) Yalow, R. S., and Berson, S. A.: Use of K^{42} Tagged Erythrocytes in Blood Volume Determinations, Science **114**:14, 1951. (*g*) Berlin, N. I.; Hyde, G. M.; Parsons, R. J., and Lawrence, J. H.: The Blood Volume in Various Medical and Surgical Conditions, New England J. Med. **247**:675, 1952. (*h*) Kruger, S.; Baker, L., and Mosiman, W. D.: Repeated Blood Volume Determinations in Bleeding Peptic Ulcer, Gastroenterology **21**:516, 1952. (*i*) Parsons, W. H.; Williams, W. T., and Forsythe, L. J.: The Clinical Significance of Blood Volume Determinations, Ann. Surg. **135**:791, 1952. (*j*) Shock Syndrome, edited by Miner, R. W.: Ann. New York Acad. Sc. **55**:455-542, 1952.

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16. Gross, R., and Schwarzkopf, B.: Vorschläge zur Zählung der sogenannten vitalgranulierten Erythrozyten (Retikulozyten), Acta haemat. **7**:106, 1952.

17. Sharp, J.; Feinmann, E. L., and Wilkinson, J. F.: A Method of Enumeration of Individual Marrow Elements for Research Purposes, Biometrics **8**:105, 1952.

18. Khalifa, A. A., and Salar, M. K.: A Spectrophotometric Method for the Detection of Blood Stains, Nature, London **169**:461, 1952.

19. Bernhard, W.: Electron Microscope Studies on Thin Sections of Human Erythrocytes, Nature, London **170**:359, 1952.

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After separation of erythrocytes from blood by addition of high molecular weight dextran, 80% recovery of the platelet total is obtained by centrifugation of the plasma in the presence of surface-active agents.[23] Addition of polyvinylpyrrolidone (Kollidon or Periston) to heparinized blood aids in the preservation and concentration of living leucocytes and platelets.[24] Other methods for separation and purification of leucocytes and platelets are reviewed.[25] A comparison of the Wright and the supravital staining techniques confirms the advantages afforded by the latter in more accurate recognition of the monocytic elements.[26] Lymph node aspiration is recommended as a relatively simple procedure which often provides diagnostic data in Hodgkin's syndrome, lymphosarcoma, lymphadenitis, and metastatic malignant conditions.[27] The use of rabbit antiserum which is specific for chemically proved Bence-Jones protein provides a sensitive aid to the diagnosis of multiple myeloma.[28]

Irradiation

Immediate Effects.—Most of the recent reports on the acute irradiation syndrome are based on information of the bombing in Hiroshima and Nagasaki and from research accidents occurring at Los Alamos. A most comprehensive review on the acute irradiation syndrome has been published by Hempleman and his associates in a separate issue of the *Annals of Internal Medicine* (March, 1952).[29] Many of the resulting symptoms are produced by hematologic changes.

The general order of the decreasing sensitivity of the hemopoietic cells to irradiation is as follows: medium lymphocytes and polychromatophilic erythrocyte precursors, small lymphocytes, megakaryocytes, large lymphocytes, basophilic leucocytes, eosinophilic leucocytes, proerythroblasts, neutrophilic leucocytes, primitive reticulum cells, plasmocytes, and connective tissue cells.[30]

Since lymphocytes are the most sensitive of the peripheral formed elements, certain observations of them have proved to be valuable aids in detecting small amounts

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of radiation. When the supravital staining technique is used, a striking increase in the number of refractive neutral red bodies in the cytoplasm of the circulating lymphocytes of those persons exposed to radiation is observed.[31] This is perhaps the most sensitive means currently available for the objective determination of irradiation effects. In cyclotron workers there was found a direct relation between the extent of exposure and the frequency of lymphocytes with bilobed nuclei.[32] The bilobed nucleated lymphocyte enumeration has been proposed as a valuable adjunct to physical monitoring of irradiation. Chamberlain and co-workers evaluated the use of total leucocyte counts as an index of radiation exposure and concluded that it does not give an accurate description of exposure.[33] An index of the hemorrhagic state induced by irradiation in dogs and rats correlates quantitatively the blood-platelet and the lymph-erythrocyte levels.[34]

In irradiated dogs transfused red cells survive longer than the recipient's own cells.[35] When a modified Ashby technique is used in rabbits, the survival time of irradiated donor erythrocytes is shorter than that of cells from nonirradiated donors.[36] The mechanism of the shortened survival time is not understood. Furth and his co-workers, in a series of publications, found that in irradiated animals a large amount of whole blood disappears from the major circulation within 24 hours.[37] This was interpreted as being caused by an increased capillary permeability. The erythrocytes escape into the tissue and lymph spaces and ultimately find their way, via the lymphatic duct, back into the general circulation. It is possible that this diversion results in damage to the erythrocytes which causes an increased rate of their destruction. Injections of concentrated suspensions of blood platelets eliminate large scale diversion of erythrocytes into the lymph after intense irradiation.[38]

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31. Dickie, A., and Hempelmann, L. H.: Morphologic Changes in the Lymphocytes of Persons Exposed to Ionizing Radiation, J. Lab. & Clin. Med. **32**:1045, 1947.

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Under the same conditions erythropoietic tissue is significantly less sensitive to experimentally induced radiation injury than is the myelopoietic tissue of the same animal.[38a]

It has been well established that, under certain circumstances, total body roentgen-irradiation inhibits antibody production. The immune response is diminished in mice by radiation from radioactive cobalt (Co^{60}).[39] Rabbits receiving 500 and 800 r total body irradiation also show a similar inhibition of antibody production. However, if the spleen is protected with lead shielding, even if it is removed 24 hours after irradiation, antibody production is retained.[40]

Long-Range Effects.—An increased incidence of leukemia has been observed, not only in radiologists but also in physicians and dentists using fluoroscopy routinely.[41] Data obtained from Hiroshima and Nagasaki also reveal increased incidences of leukemia in the population exposed to secondary irradiation.[42] Further discussion on these aspects of irradiation is on page 421.

Protection and Postirradiation Therapy.—Numerous physiologic methods and chemicals have been found to afford protection from intense irradiation. Among these are cysteine, dimercaprol (BAL; British-Anti-Lewisite; 2,3,1- dimercaptopropanol), glutathione, sodium nitrite, alcohol, cyanide, carboxylic and amino acids, vitamin C, glucose, estrogens, cortisone, deoxycorticosterone, whole liver (other than known factors of the vitamin B group), splenic shielding, intraperitoneal implantation of splenic tissue, embryo and bone marrow suspensions, lowered temperature, reduced oxygen tension, and antibiotics.[43]

38a. Valentine, W. N., and Pearce, M. L.: Studies on the Radiosensitivity of Bone Marrow: I. The Relative Sensitivity of Erythroid and Myeloid Elements, Blood **7**:14, 1952; II. The Effect of Large, Repeated Whole Body Irradiation Exposure on Hematopoiesis, ibid. **7**:14, 1952; III. The Dynamics of Erythrocyte Regeneration After Hemorrhage and Irradiation, ibid. **7**:207, 1952.

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Flavonoids and the leucocytosis-promoting factor do not protect the experimental animal from irradiation.[44]

Knowledge of therapeutic measures for irradiation is meager. Lipoprotein-nucleic acid complex (Reticulose) was found to be of value.[45] Irradiated animals have been treated with cross transfusions and antibiotics with some degree of success.[43e] Cysteine is of no protective value in irradiated rabbits.[46] No increase has been found in the survival of irradiated dogs treated by whole blood transfusion.[47] Cortisone does not afford protection to the irradiated animal and does not aid in marrow regeneration but actually has proved to be detrimental to recovery.[48]

Toxic Depressants

Of the toxic depressants chloramphenicol (Chloromycetin) has received the most attention.[49] Isolated from soil micro-organisms in Venezuela,[50] it was later synthesized.[51] In the molecule of chloramphenicol is the notorious nitrobenzene radical. Indiscriminate and excessive use of the drug causes aplastic anemia, thrombocytopenia, and/or granulocytopenia. Experimentally it also has a stimulating effect on the reticuloendothelial system of rats,[52] suggesting that the effect of a hemolytic component may be superimposed on the hypoplastic effect.

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Chronically ill, debilitated, and aged patients seem particularly susceptible to the toxic action of chloramphenicol. However, fatalities are reported in all age groups.[53] Of 10 cases reported by Hargraves, 7 terminated fatally. Purpura is frequently the presenting sign, with accompanying pancytopenia in the peripheral blood. [49g]

The urgency of the situation resulted in the National Research Council calling a conference to investigate these and other reports of fatalities.[51] The conference agreed that when continuous or intermittent chloramphenicol therapy is required, adequate blood studies must be made. Packages containing the drug should be labeled as to the dangers of its unprescribed and indiscriminate use.

It is doubtful whether chloramphenicol offers any advantages over aureomycin and oxytetracycline (Terramycin), except in the treatment of typhoid fever.[49h] It can be given with a certain calculated risk, but it is not a panacea.[54]

Hypoplastic marrow has been observed after administration of methyl-5,5-phenylethylhydantoin (Mesantoin) [55] and thiosemicarbazone.[56] Pancytopenia has been noted also during the treatment of thyrotoxicosis with the drugs of the thiourea group (uracil, thiouracil, thiorea),[57] which is possibly due to an interference with the normal uracil metabolism. Other incriminated agents are radioactive colloidal gold,[58] many coal tar derivatives,[59] antihistaminic drugs,[60] and the vehicle of cortisone.[61] Miliary tuberculosis involving the bone marrow has been associated with pancytopenia.[61a]

Drugs causing predominantly a depression of granulocyte formation in the marrow are methimazole (Tapazole, an antithyroid drug),[62] sulfonamides,[63] sulfadiazine,[64] bismuth glycolylarsanilate (Milibis, an antiamebic drug),[65] isoniazid (iso-

53. Footnote 49*a*, *e*, and *h*.

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nicotinic hydrazide),[66] aminopyrene,[67] phethenylate sodium (Thiantoin),[68] mercurial diuretics (mersalyl),[69] a phenothiazine (Diparcol, a drug used for Parkinson's syndrome),[70] carinamide,[71] and phenylbutazone (Butazolidin).[72]

Platelet depressions are caused by the following: allyl-isopropyl-acetyl-carbamide (Sedormid),[73] quinidine,[74] marbadal (sulfathiourea salt of marfanil), aminopyrine (Pyramidon),[75] sulfisoxazole (Gantrisin),[76] and arsenic.[77]

Other chemical extrinsic factors are also implicated. DDT (dichlorodiphenyl-trichloroethane) produces platelet depression.[78] Workers in mercury mines and smelting plants show no pathologic change in their blood picture.[79]

Corticotropin (ACTH) and Cortisone

Techniques.—The use of the eosinopenic response during the administration of corticotropin (ACTH) as a criterion indicating an intact adrenal cortex has focused attention on (1) the diurnal variation in the number of circulating eosinophile cells in normal and diseased persons[80] indicating that eosinophile counts should be made at the same time each day,[81] and (2) methods for counting eosinophile cells.[80b] An

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analysis of the sampling errors in the direct method suggests modifications in techniques.[82] Several different solutions produce satisfactory results.[83] The chemistry of the staining reaction and the use of a fixed thin blood film technique have been detailed.[84] A capillary-tube technique offers ease of collection, accuracy, and reproducibility of results.[86b] Six hourly intramuscular injections of equal amounts of corticotropin elicit the most consistent eosinopenic response.[85]

Experimental Findings.—The new interest in the adrenal cortex-eosinophile relation has directed attention to the origin and fate of eosinophiles, the factors producing eosinopenia, and conditions affecting the activity and production of the adrenocortical steroids.[86] The fate of the eosinophile following corticotropin administration continues to be conjectured.[87] Most interesting observations have been made by Padawer and Gordon.[88] In response to epinephrine the nucleus of the normal eosinophile is fragmented and is no longer stainable with Giemsa stain. The cytoplasmic granules become densely packed, forming masses that stain intensely with eosin or phloxine. All this is accompanied by shrinkage of the cell. There is a marked increase in the number of eosinophilic leucocyte fragments in the peripheral blood.

During prolonged administration of large amounts of adrenocortical hormones, an increase in erythrocytic elements is produced in the bone marrow of mice [89] and in rabbits.[90] Monocytes are decreased to the same degree as the circulating lymphocytes. In humans the platelets in the pheripheral blood show a significant temporary decrease.[91] Oral cortisone administration produces an increase in neutrophiles and

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a decrease in lymphocytes and eosinophiles.[92] Sensitizing principles of certain corticotropin preparations cause bone marrow depression.[61] Common chemical characteristics of all steroids producing eosinopenia have been described.[93] Other chemicals similarly studied for their eosinopenic and/or lymphopenic effect are amethopterin [94] and insulin.[95]

Clinical Observations.—Stress stimuli producing eosinopenia are precipitated by psychological situations, as observed in students before an examination,[96] in psychopathic patients,[97] in surgical shock,[98] and in cardiovascular stress [99]; however, the eosinopenia is not consistent enough to be of diagnostic value in infection,[100] in fever,[101] in pregnancy, and in labor.[102] In chronic alcoholism [103] no difference from the normal response has been detected with either corticotropin or epinephrine tests.

Therapy.—Experimental therapy with corticotropin and cortisone in nearly the entire spectrum of blood diseases has been reported. In acute leukemias these hormones are valued adjuncts to treatment with the folic acid antagonists.[104] The extent to which they affect life expectancy has not been definitely ascertained.[105]

92. Kowalski, H. J.; Reynolds, W. E., and Rutstein, D. D.: Changes in White Blood Cell Counts After Administration of Cortisone Acetate to Healthy Ambulatory Individuals, Proceedings American Federation Clinical Research, National Meeting, Atlantic City, N. J., May 4, 1952.

93. Halberg, F.: Some Correlations Between Chemical Structure and Maximal Eosinopenia in Adrenalectomized and Hypophysectomized Mice, J. Pharmacol. & Exper. Therap. **106**:135, 1952.

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104. (*a*) Stickney, J. M., and Mills, S. D.: Corticotropin and Cortisone in Blood Diseases in Children, J. A. M. A. **150**:1278, 1952. (*b*) Treatment of Leukemia, Cornell Conference on Therapy, New York J. M. **52**:2910, 1952.

105. Bierman, H. R.; Kelly, K. H.; Petrakis, N. L., and Shimkin, M. B.: Leukemia, Duration of Life of Children Treated with Corticotropin and Cortisone, California Med. **77**:238, 1952. Tivey, H.: Prognosis for Survival in the Leukemias of Childhood, Pediatrics **10**:48, 1952.

Some benefit from these drugs is also evident in certain cases of chronic lymphocytic leukemia, lymphosarcoma, and multiple myeloma.[106] They are of meager usefulness in Hodgkin's disease.[107] Remissions have been secured in acquired hemolytic anemias,[108] except in a case due to sulfapyridine.[109] A moderately good response is effected in acute immunopancytopenia.[110] Good results have been reported also in the treatment of sickle cell anemia,[111] in some cases of erythroblastosis,[112] and in one case of thalassemia major.[111] Improvement in the nutritional state of patients with nontropical sprue is noted following treatment with corticotropin and cortisone.[113] Only rare response is effected in hypoplastic anemia.[108b] Good results have been inferred in a drug-induced granulocytopenia,[114] but no improvement occurred in one case of panmyelopathy.[115] In acute vascular purpura, results are often striking.[108b] The results in idiopathic thrombocytopenic purpura are quite variable.[116] A general average response is approximately 50%.

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Hematologic Problems in Pregnancy

Many hematologic syndromes are associated with pregnancy. These are scattered throughout this review. Regrouping of these references here emphasizes the extensiveness of this relation. Pregnancy and the following hematologic problems have been reviewed: the "spurious," "erroneous," or "relative" anemias [12a,b]; macrocytic anemia [117]; erythroblastosis fetalis [118]; iron deficiency anemia and iron metabolism [119]; sickle cell anemia [120]; paroxysmal cold hemoglobinuria [121]; sludged blood [122]; hypoplastic anemia [123]; methemoglobinemia [124]; leukemia [125]; lupus ery-

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(Footnotes continued on next page)

thematosus disseminatus[126]; Hodgkin's disease[127]; thrombocytopenic purpura[128] and irradiation.[41b]

Bone Marrow

The increasing importance of marrow studies in clinical medicine has been repeatedly emphasized.[129] Frequently the study of a single marrow aspiration does not give an adequate evaluation of the total picture. Thus aspirations from multiple sites, such as sternum, anterior and posterior iliac crest, vertebra, femur, and ribs, may aid in the quantitative appraisal.[129b,c] The advantages of studying an architecturally intact marrow specimen are afforded by a relatively simple rib resection technique.[130]

The finding of granulomatous lesions in marrow aspirations frequently confirms the diagnosis of tuberculosis, sarcoidosis, histoplasmosis, infectious mononucleosis, granulomatous hepatitis, and Hodgkin's disease. Rarely, the marrow findings are the primary means of establishing the diagnosis.[129d] Bone marrow studies in 107 patients with acute infectious diseases showed hyperplasia and myeloid immaturity to be the most characteristic findings.[129a] Pancytopenia may be caused by miliary tuberculosis involving the bone marrow.[129h] A case of neuroblastoma was presumptively diagnosed by finding the tumor cells in the bone marrow.[129f] Metastatic prostatic carcinoma cells were demonstrated in the marrow in 33% of the cases of Clifton and his associates.[129g] It is recommended that marrow examination should be done in patients with prostatic carcinoma for whom radical surgery is being considered.

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131. Footnote deleted.

Routine cultures of the marrow for Histoplasma capsulatum are of no appreciable clinical value.[132]

Hypophysectomy in the rat results in a number of differential changes, which are detailed in the original article.[133] No correlation has been noted between marrow temperatures and the various cell types in miscellaneous hematologic dyscrasias.[134] A positive cytoplasmic reaction has been obtained by a modified technique of plasmal reaction in the following cells from human and rat blood and hemopoietic organs: megakaryocytes, platelets, neutrophiles, eosinophiles, lymphocytes, monocytes, plasmacytes, early erythroblasts, and reticular cells.[135] Four different nonhumoral antigenic components have been demonstrated in bone marrow; however, none are strictly specific to this organ.[136]

RED BLOOD CELLS

Erythrocyte Production and General Observations

The human red blood cell undergoes a progressive transformation before it reaches its terminal functional state. A wide variety of physical and chemical observations have been made at various phases in this transformation.

The normal marrow picture in the newborn human infant from birth to three months was studied by Gairdner and co-workers.[137] The factors responsible for the changing red cell picture after birth were found to be primarily in the erythropoietic activity, which was governed by the arterial oxyhemoglobin level, and in the effect of body growth.

True erythropoietic stimulation can be achieved experimentally by only three conditions: anoxic anoxia, anemic anoxia, and excessive cobalt. The hypothesis of humoral mediation by "hemopoietin" or similar substances appears to be more fundamentally sound than that of direct anoxic stimulation.[138]

It has been concluded from studies of the circulating red cells in the chick embryo[139] that there is an overlapping of growth and differentiation in primitive cells. A reversibility between the normoblastic and megaloblastic series was suggested by a study using a refined technique of cell culture.[140]

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132. Schwartz, S. O., and Barsky, S.: Report of 193 Marrow Biopsy Specimens Cultured for Histoplasma Capsulatum, Blood **7**:545, 1952.

133. Landau, D., and Gordon, A. S.: The Effects of Hypophysectomy on the Respiration and Cellular Components of the Bone Marrow of the Rat, Endocrinology **5**:157, 1952.

134. Petrakis, N. L.: Temperature of Human Bone Marrow, J. Applied Physiol. **4**:549, 1952.

135. Mota, I.; Yoneda, S., and Rabinovitch, I.: Plasmal Reaction in the Blood and Hemopoietic Organs, Proc. Soc. Exper. Biol. & Med. **81**:338, 1952.

136. Bjorklund, B.: Serological Analysis of Components in Hemopoietic Tissue, Proc. Soc. Exper. Biol. & Med. **79**:324, 1952.

137. Gairdner, D.; Marks, J., and Roscoe, J. D.: Blood Formation in Infancy-Normal Erythropoiesis, Arch. Dis. Childhood **27**:214, 1952; Blood Formation in Infancy-Normal Bone Marrow, ibid. **27**:128, 1952.

138. Grant, W. C., and Root, W. S.: Fundamental Stimulus for Erythropoiesis, Physiol. Rev. **32**:449, 1952.

139. O'Connor, R. J.: Growth and Differentiation in the Red Blood Cells of the Chicken Embryo, J. Anat. **86**:320, 1952.

140. Lajtha, L. G.: Culture of Human Bone Marrow in Vitro: The Reversibility Between Normoblastic and Megaloblastic Series of Cells, J. Clin. Path. **5**:67, 1952.

In studying physical characteristics of the erythrocyte, the flicker phenomenon (vibratory movements in erythrocytes) has been used as a test for their activity under different conditions. This action was found to be closely related to the metabolism and shape transformations of the erythrocyte.[141]

Further study of the surface of the mammalian erythrocyte with the electron microscope has demonstrated that the contents of the red cell offer structural support to the surface and form a part of its layers.[142]

In chemical analysis of bone marrow,[143] the deoxyribonucleic acid phosphorus content was found to be increased in early erythroblasts and decreased in late erythroblasts. Recent studies demonstrate that human erythrocytes synthesize acetylcholine. This synthesis may be related to some general phenomenon, such as control of changes in permeability.[144]

Chloride distribution between the inside and outside of erythrocytes depends primarily on pH and not on the state of cell metabolism.[145] Under controlled conditions ascorbic acid moves in or out of the erythrocyte in vivo.[146]

Fluoride and iodoacetate cause changes associated with inhibition of cellular metabolism.[147] Their effects on the concentration and turnover of radioactive phosphorus (P^{32}) in several acid-soluble organic phosphorus compounds in human erythrocytes have been studied,[148] and the hypothesis that inorganic phosphate enters the red cell by the formation of adenosine triphosphate at the cell membrane has been suggested.

Electron micrograph studies of the effects of various experimental treatments on erythrocytes have shown that there are essentially four phases of modification in the integrity of the red blood cell structure. In order of severity, these are craters, spicules (found only on erythrocytes having sawtooth points on their periphery; the spicules are the sawtooth points flattened out on the surface of the cell), hematexodies (fine filaments swollen at their extremities or spherical granules free or attached to the cell), and aureolas (around the entire cell). In the untreated cell only a few small craters are found. Treatments such as washing in isotonic sodium chloride solution, heating to 56 C., storing at 4 C., agglutination by heavy metals, and agglutination by immune serum (in this order) increased the effects above.

141. Weis-Fogh, J.: The Flicker Phenomenon in Erythrocytes Used as a Test for Activity of the Erythrocytes Under Different Conditions, Anat. Rec. **112**:466, 1952.

142. Latta, H.: The Surface of the Mammalian Erythrocyte: An Electron Microscope Study of the Effect of Lipid Solvents, Fixatives, Hypotonicity, and Hemolysin (Amboceptor) and Complement, Blood **7**:508, 1952.

143. Menten, M. L., and Willms, M.: Changing Values of Nucleic Acid of Cells in Bone Marrow During Development of Red Blood Cell, A. M. A. Arch. Path. **54**:343, 1952.

144. Holland, W. C., and Greig, M. E.: The Synthesis of Acetylcholine by Human Erythrocytes, Arch. Biochem. **39**:77, 1952.

145. Harris, E. J., and Maizels, M.: Distribution of Ions in Suspensions of Human Erythrocytes, J. Physiol. **118**:40, 1952.

146. Golden, R., and Sargent, F.: The Passage of Ascorbic Acid Across the Membrane of the Human Erythrocyte, Arch. Biochem. **39**:138, 1952.

147. O'Connor, R. J.: Carbohydrate Metabolism and Cell Division in Developing Red Blood Cells, Brit. J. Exper. Path. **33**:462, 1952.

148. Gourley, D. R. H.: Glycolysis and Phosphate Turnover in the Human Erythrocyte, Arch. Biochem. **40**:13, 1952.

The action of trypsin, on the other hand, entails the progressive disappearance of the various figures, giving a smooth or slightly granulous appearance to the surface of the cell.[148a]

Erythrocyte Sedimentation Rate

Recent investigations suggest that an increased erythrocyte sedimentation rate is dependent on increased fibrinogen and/or globulins.[149] The Westergren and Wintrobe methods are the most widely accepted means of measuring the erythrocyte sedimentation rate. Comparison of the two methods in 52 patients showed normal Wintrobe but elevated Westergren readings in 6 persons. The Westergren method correlated with the clinical condition of the patients and was thought to be superior. The lesser sensitivity of the Wintrobe method was attributed to the oxalate anticoagulant.[150]

When normal cells are diluted in their own plasma, the erythrocyte sedimentation rate is increased. On the basis of this observation, it has been presumed that the erythrocyte sedimentation rate is increased in anemia. Recent studies indicate that not only dilution but also anisocytosis and plasma factors influence the erythrocyte sedimentation rate.[151] Increased erythrocyte sedimentation rate in hypochromic anemia is significant because it indicates the presence of complicating factors and is not due to the anemia alone.[152]

In myocardial infarction, elevated erythrocyte sedimentation rate after the 36th day indicates extracardiac pathology.[153] It is adjudged also to be a more accurate indication of the local process in cholecystitis than is any other test or clinical finding.[149] Decreased erythrocyte sedimentation rate offers the best means of differentiating allergy from infection.[154] The erythrocyte sedimentation rate is of little value in the diagnosis of malignant disease.[155]

Blood Types, Storage, Substitutes, and Transfusion

Blood Types.—In spite of the tremendous expansion of knowledge concerning blood types[156] the continued necessity for restandardization of techniques employed

148a. Ponder, E.; Bessis, M.; Bricka, M., and Breton-Gorius, J.: Modifications de la surface des érythrocytes par différentes agressions (et particulièrement durant l'agglutination) étudiées par microscopie électronique, Rev. hemat. **7**:550, 1952.

149. Hewlett, T. H.: The Sedimentation Rate in Acute Cholecystitis, U. S. Armed Forces M. J. **3**:1267, 1952.

150. Goldberg, A., and Conway, H.: Observations on the Methods of Measuring the Erythrocyte Sedimentation Rate, Brit. M. J. **2**:315, 1952.

151. Poole, J. C. F., and Summers, G. A. C.: Correction of ESR in Anaemia: Experimental Study Based on Interchange of Cells and Plasma Between Normal and Anaemic Subjects, Brit. M. J. **2**:353, 1952.

152. Rogers, K. B.: The Effect of Hypochromasia on the Specific Gravity and Sedimentation of Red Cells, Brit. M. J. **1**:1109, 1952.

153. Plotz, M.: Sedimentation Rate in Myocardial Infarction, Am. J. M. Sc. **224**:23, 1952.

154. Van Ufford, W. J. Q.: The Blood Sedimentation Rate in Allergic Patients, Internat. Arch. Allergy & Appl. Immunol. **3**:136, 1952.

155. Beresford, O. D.: The Role of the Sedimentation Rate in the Diagnosis of Malignancy, Canad. M. A. J. **67**:347, 1952.

156. Allen, F. H., Jr.: Importance of the Blood Groups in Laboratory and Clinical Medicine, New England J. Med. **247**:380, 1952. Stratton, F.: The Human Blood Groups, Nature, London **170**:821, 1952.

for typing and cross matching is borne out by reports of transfusion reactions.[157] New methods for typing large numbers of persons were suggested.[158]

Additional information regarding red blood cell antigens includes a new blood character related to the ABO system,[159] a second example of anti-Cellano,[160] occurrence of several of the classic human blood group antigens in the chimpanzee,[161] the separation of the H and Le^a (Lewis) factors and characterization of their physical and chemical properties,[162] and the reactivity of the O and H receptors of erythrocytes from Group O cord bloods.[163]

Inheritance of blood group antigens [164] and the expanded medicolegal application of blood grouping tests have been reviewed.[165] Analysis of previously reported data suggests a possible genetic rather than serologic role of the ABO blood group in general reproduction.[166] Several cases of erythroblastosis fetalis have been attributed to in utero sensitization with antibodies to A and B.[167]

Knowledge of blood group systems has been applied to problems in anthropology in studies on Northern Sudanese,[168] Eskimos,[169] Yemenite Jews,[170] and various populations in Borneo.[171]

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157. Error in Blood Transfusion, Editorial, Lancet **1**:879, 1952. Dodge, O. G.: A Comparative Study of Direct Matching Techniques in Blood Transfusion, J. Clin. Path. **5**:102, 1952.

158. (*a*) Bende, Y. M.; Deshpande, C. K.; Bhatia, H. M.; Sanger, R.; Race, R. R.; Morgan, W. T. J., and Watkins, W. M.: A "New" Blood-Group Character Related to the ABO System, Lancet **1**:903, 1952. (*b*) Nelson, W. C.: A Method for Training Civilians in Blood Grouping Tests in the Event of an Atomic Disaster: With Pilot Test Results, Am. J. Clin. Path. **22**:958, 1952.

159. Hirszfeld, L.: A "New" Blood-Group Character Related to the ABO System, correspondence, Lancet **2**:826, 1952. Bende and others.[158a]

160. Levine, P.; Kuhmichel, A. B., and Wigod, M.: A Second Example of Anti-Cellano (Anti-K), Blood **7**:251, 1952.

161. Wiener, A. S.: Blood Group Factors in Anthropoid Apes and Monkeys: I. Studies on a Chimpanzee, "Pan," Am. J. Phys. Anthropol. **10**:372, 1952.

162. Annison, E. F., and Morgan, W. T. J.: Studies in Immunochemistry: II. The Isolation and Properties of the Human Blood-Group H Substance, Biochem. J. **52**:247, 1952. Kekwick, R. A.: Physicochemical Examination of Blood-Group H Substance, ibid. **52**:259, 1952. Annison, E. F., and Morgan, W. T. J.: Isolation and Properties of Lewis (Le^a), Human Blood Group Substance, ibid. **50**:460, 1952.

163. Watkins, W. M.: The O and H Blood Group Characters in the Newborn, Brit. J. Exper. Path. **33**:244, 1952.

164. Matson, G. A., and Koucky, R. W.: Blood Group Factors, Inheritance of the Blood Group Antigens, Minnesota Med. **35**:529, 1952.

165. Blood-Groups in Disputed Paternity, editorial, Lancet **1**:296, 1952. Medicolegal Application of Blood Grouping Tests, editorial, J. A. M. A. **149**:666, 1952.

166. Allan, T. M.: Blood Groups and Reproduction, Lancet **1**:102, 1952.

167. Phansomboon, S., and Pollack, O. J.: A Study on the A Factor as a Cause of Hemolytic Disease in Premature Babies, Brit. M. J. **1**:1170, 1952. Berger, E., and Steurenthaler, W.: Icterus gravis neonatorum bei AO-Unverträglichkeit, Ann. pædiat. **178**:343, 1952.

168. Brooks, P. J.; Garner, K. E.; Ikin, E. W.; Mourant, A. E., and Drysdale, A.: The Blood Groups of the Northern Sudanese, Ann. Eugenics **17**:75, 1952.

169. Ahrengot, V., and Eldon K.: Distribution of ABO-MN and Rh Types Among Eskimos in South-West Greenland, Nature, London **169**:1065, 1952.

170. Dreyfuss, F.; Ikin, E. W.; Lehmann, H., and Mourant, A. E.: An Investigation of Blood-Groups and a Search for Sickle-Cell Trait in Yemenite Jews, Lancet **2**:1010, 1952.

171. Graydon, J. J.; Simmons, R. T.; Semple, N. M.; Clapham, L. J., and Wallace, E. H.: Blood Genetics of Various Populations in Borneo, M. J. Australia **1**:694, 1952.

Investigations on the use of extracts of certain beans as blood-typing substances have been continued.[172] Successful differentiation of the subtypes of Type A was accomplished with an extract of Dolichos biflorus [173]; this substance appears to have a different serologic specificity from that of the Classic Forssman heterophile antibody.[174]

Storage and Preservation.—Advantages of blood collection in hemorepellent plastic bags include (1) avoidance of anticoagulants in blood used six hours or less after collection, (2) lower cost, (3) ease of plasma separation, (4) reduction of contamination, and (5) lessened danger of air emboli.[3]

Research in blood storage problems has been directed toward slowing cell metabolism by various freezing methods or by disturbing the optimum ionic concentration. Seventy per cent of erythrocytes stored in glycerol at —79 C. were recovered after periods of six to nine months; however, viability studies are still in progress.[175] Storage at —15 C. is less promising.[176] Addition of a phenothiazine derivative (Phenergan) does not prolong storage life.[177]

Oxygenation of blood during storage proved to be promising. The need for valid in vitro laboratory tests to predict in vivo results is a paramount problem.[178] The use of decalcified blood is suggested for instances in which low sodium and potassium concentration is desirable.[3] The "storage lesion" of the erythrocyte appears to be different from normal cell senescence; also, biochemical characteristics are reversed upon reintroduction of the stored erythrocyte into the blood stream.[179]

Plasma Fractions and Volume Expanders.—An extensive review of a conference on shock syndrome by the New York Academy of Sciences includes an excellent coverage of "Plasma and Volume Expanders." Reference to the original article is suggested.[12j] Maintenance of blood volume for varying periods of time has been accomplished with a number of substances.[180] They do not, of course, reduce the need for whole blood.[181] Dextran has proved effective in clinical shock.[182] No ill

172. Cazal, P., and Lalaurie: Recherches sur quelques pyto-agglutinines spécifiques des groupes sanguins ABO, Acta haemat. **8**:73, 1952.

173. Bird, G. W G: Relationship of the Blood Sub-Groups A_1, A_2 and A_1B, A_2B to Haemagglutinins Present in the Seeds of Dolichos Biflorus, Nature, London **170**:674, 1952.

174. Bird, G. W. G.: Anti-A Haemagglutinins in Seeds, J. Immunol. **69**:319, 1952.

175. Sloviter, H. A.: Recovery of Human Red Cells After Prolonged Storage at -79° C. Nature, London 169:1013, 1952.

176. Mollison, P. L.; Sloviter, H. A., and Chaplin, H., Jr.: Survival of Transfused Red Cells Previously Stored for Long Periods in the Frozen State, Lancet **2**:501, 1952.

177. Chaplin, H.; Crawford, H.; Cutbush, M., and Mollison, P. L.: The Effects of a Phenothiazine Derivative (RP. 3300) on Red Cell Preservation, J. Clin. Path. **5**:91, 1952.

178. Pennell, R. B.: Preservation of Whole Blood and Red Cells, Internat. Rec. Med. & Gen. Practice Clin. **165**:137, 1952.

179. Stevens, A.; Gabrio, B.; Czajkowski, R., and Finch, C.: Observations on the Storage Lesion of the Erythrocyte, abstracted J. Clin. Invest. **31**:665, 1952.

180. Meyer, L. M.; Berlin, N. I.; Hyde, G. M.; Parsons, R. J., and Whittington, B.: Changes in Blood Volume Following Administration of Dextran, Digest Treatment **3**:855, 1952.

181. (*a*) Bloom, W. L.: Dextran: A Polysaccharide for the Expansion of Plasma Volume, Digest Treatment **3**:855, 1952. (*b*) Pulaski, E. J.: The Chemical Status of Dextran, P.V.P. and Gelatine Products, Quart. Rev. Med. **10**:44, 1952. (*c*) Anderson, L. S.: Blood Substitutes in Atomic Warfare: A Review of the Present Position, Canad. J. Pub. Health **43**:235, 1952.

182. Wilson, J. S.; Estes, E. H., Jr.; Doyle, J. T.; Bloom, W. L., and Warren, J. V.: The Use of Dextran in the Treatment of Blood Loss and Shock, Am. J. M. Sc. **223**:364, 1952.

effects have been noted,[183] and renal function is not altered.[183a] Hydrolyzed dextran has no effect on typing or cross matching.[183c] Polyvinylpyrrolidone (Kollidon, Periston, or P.V.P.), when used as a plasma extender, is deposited in large amounts in organs of the reticuloendothelial system and in the abdominal fatty tissues.[184] The amount deposited increases with molecular weight.[185] Dextran appears to decrease capillary fragility to a greater extent than polyvinylpyrrolidone.[186]

The clinical use of serum albumin, bimetal combining globulin, gamma globulin, and coagulation fraction of plasma has been reviewed.[187]

Transfusions.—A most conservative estimate of transfusion mortality is 1 in 3,000 transfusions. For the approximately 3,000,000 transfusions in this country per year there would be 1,000 deaths. The risk involved is believed sufficiently great to contraindicate transfusions unless the purposes are absolutely clear. The reasons for transfusion deaths include (1) human error, (2) storage mishaps, (3) severe hemolytic reactions due to previous sensitization of the patient to one of the rare blood groups, (4) circulatory overload, (5) contamination of the blood, and (6) serum hepatitis.[188]

Simultaneous exsanguination and transfusion in severe anemia was reported by Ward.[189] An even more spectacular procedure, of cross transfusion between patients and normal donors, produced death in one of six donors and somewhat less severe reactions in others.[190]

The danger of transmission of homologous serum jaundice with pooled plasma [191] and the frequency of immunization of Rh-negative women by transfusion with Rh-positive blood [192] have been repeatedly stressed. Abnormal bleeding in the form of profuse oozing from surgical wounds or mucous membranes has been added to the deleterious effects of transfusions with incompatible blood.[193] Rutin, cortico-

183. (*a*) Marshall, L. H.; Hanna, C. H.; Specht, H., and Neal, P. A.: Blood Changes of Normal Dogs During Chronic Blood Volume Expansion with Dextran, Proc. Soc. Exper. Biol. & Med. **79**:363, 1952. (*b*) Hammarsten, J. F., and Heller, B. I.: The Effects of Dextran in Subjects with Normal Blood Volumes and in Subjects after Bleeding, J. Lab. & Clin. Med. **40**:807, 1952. (*c*) Roche, P., Jr.; Dodelin, R. A., and Bloom, W. L.: Effect of Dextran on Blood Typing and Crossmatching, Blood **7**:373, 1952.

184. Brass, K.: Morphologische Befunde bei Mensch und Kaninchen nach wiederholter Periston-(Kollidon-) Zufuhr, Frankfurt. Ztschr. Path. **63**:95, 1952.

185. Fresen, O., and Weese, H.: Das gewebliche Bild nach Infusion verschiedener Kollidonfraktionen (Periston N, Periston, Hochviskoses Periston) beim Tier, Beitr. path. Anat. **112**:44, 1952.

186. Eichholtz, F.: Versuche über Blutersatzmittel, abstracted, Arch. exper. Path. u. Pharmakol. **216**:188, 1952.

187. Janeway, C. A.: Clinical Status of Plasma Fractions, Am. J. Pharm. **124**:161, 1952.

188. Moore, C. V.: Medical Problems Created by a National Blood Program, J. A. M. A. **149**:1613, 1952.

189. Ward, T.: Exchange Transfusion in Severe Anemia, Brit. M. J. **1**:631, 1952.

190. Salisbury, P. F.; Bolomey, A. A., and Miller, J. H.: Cross Transfusion: III. Clinical Experiences with 6 Cases, Am. J. M. Sc. **223**:151, 1952.

191. Conley, C. L.: Untoward Reactions from Blood Transfusions, Maryland M. J. **1**: 547, 1952.

192. A Danger of Blood Transfusion, annotations, Brit. M. J. **2**:986, 1952.

193. Friesen, S. R.; Harsha, W. N., and McCroskey, C. H.: Massive Generalized Wound Bleeding During Operation with Clinical and Experimental Evidence of Blood Transfusion Reactions, Surgery **32**:620, 1952.

tropin (ACTH), and cortisone are claimed to be effective in counteracting reactions to incompatible blood.[194] Full evaluation awaits further investigation.

Transfusion units, consisting of human erythrocytes packed by dextran sedimentation with added cholinesterase and streptomycin, give fewer reactions than whole blood, even when stored as long as eight weeks.[195] Further evaluation is necessary.

The Anemias

Excellent general reviews on anemia have been made by Murphy[196] and Reisner.[197] Cerebral blood flow has been studied in anemic patients and found to be significantly elevated, while the cerebral oxygen consumption is moderately reduced below that of control subjects. With administration of 85 to 100% oxygen there is a reversal of these measurements, which suggests the use of oxygen as a rational emergency therapeutic measure when symptoms are present.[198] Another interesting study in pigs demonstrates that anemia stimulates intra-arterial coronary anastomoses in normal animals and occasionally protects the animals against subsequent acute coronary artery occlusion.[199] Crosby reviewed the pathogenesis of spherocytes and leptocytes (target cells).[200] The leptocyte is found in a diversity of disorders—sicklemia, thalassemia (hereditary leptocytosis), liver disease, posthemorrhagic and postsplenectomy states, iron-deficiency anemia, and severe dehydrative states.

Macrocytic Anemia.—Macrocytic anemias include both megaloblastic and nonmegaloblastic types. The following classification is used: megaloblastic: pernicious anemia, tropical sprue, idiopathic steatorrhea (nontropical sprue), nutritional macrocytic anemia (tropical macrocytic anemia), megaloblastic anemia of pregnancy, megaloblastic anemia of infancy, refractory (achrestic) megaloblastic anemia, macrocytic anemia following gastrointestinal surgery, and parasitic macrocytic anemia; nonmegaloblastic: the macrocytic anemias of liver disease, hypothyroidism, hemolytic disease, internal irradiation, and hypoplastic bone marrow. Davidson reported 136 cases of nonmegaloblastic and 577 cases of megaloblastic anemias in a series of 713 cases of macrocytic anemias.[117d] Megaloblastic anemias are not always manifested peripherally by macrocytosis.[201]

Clinical Studies: Pernicious anemia was found to be rare before 30 years of age. It has been considered in the relapsing anemias of children and young adults.

194. Schedel, F., and Schmidt, G.: Beitrag zur Herabminderung von Transfusionsgefahren, Deutsche med. Wchnschr. **77**:505, 1952. Myerson, R. M., and Clagett, A. H., Jr.: The Absence of Transfusion Reaction with ACTH and Cortisone, Delaware M. J. **24**:41, 1952.

195. Barnard, R. D.: Packed Human Erythrocyte-Plasma Esterase Units for Transfusion Purposes, New York J. Med. **52**:1283, 1952.

196. Murphy, W. P.: Anemia: Its Recognition and Management, Ohio M. J. **48**:716, 1952.

197. Reisner, E. H., Jr.: The Pathogenesis of Anemia as a Basis for Rational Treatment, New York J. Med. **52**:1645, 1952.

198. Heyman, A.; Patterson, J. L., Jr., and Duke, T. W.: Cerebral Circulation and Metabolism in Sickle Cell and Other Chronic Anemias, With Observations on the Effects of Oxygen Inhalation, J. Clin. Invest. **31**:824, 1952.

199. Zoll, P. M., and Norman, L. R.: The Effects of Vasomotor Drugs and of Anemia upon Interarterial Coronary Anastomoses, Circulation **6**:832, 1952.

200. Crosby, W. H.: The Pathogenesis of Spherocytes and Leptocytes (Target Cells), Blood **7**:261, 1952.

201. Foy, H., and Kondi, A.: Pernicious Anaemia and Macrocytic Anaemia in Uganda, Lancet **1**:416, 1952.

but many of these cases are quite possibly of idiopathic steatorrhea.[202] A higher incidence occurs in elderly persons than is generally recognized. Anemic symptoms are mild, but extra-anemic manifestations are marked.[203] The low incidence in Negroes has been questioned.[204] In addition to the classic symptoms, in patients with pernicious anemia who were in relapse fluid was sometimes retained, which caused varying degrees of edema.[205] Cited cases include pernicious anemia superseded by polycythemia [206] and pernicious anemia with Parkinsonism,[207] with optic nerve degeneration,[208] and with adrenal hypofunction.[209]

Anisocytosis and macrocytosis characterize peripheral blood films.[210] Two types of red cells have been noted. One type appears normal; the other has greater diameter but less thickness.[211] No alteration of red cell potassium levels has been found in pernicious anemia in relapse, remission, or during the period of reticulocytosis.[212] Color indices and mean corpuscular volumes vary widely in different studies.[213] Leucopenia and thrombocytopenia are often associated.[210] Serum and urine vitamin B_{12} levels are significantly lower in patients with pernicious anemia in relapse and other megaloblastic anemias that responded to vitamin B_{12} therapy.[214] Hyperbilirubenemia is frequently found in pernicious anemia.[215] These findings are in line with DeGowin's hypothesis of a coexisting hemolytic component in pernicious anemia.[216]

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202. (*a*) Conway, H.: Megaloblastic Anaemia in Young Adults, Brit. M. J. **1**:1098, 1952. (*b*) Pernicious Anemia in Childhood, Nutrition Rev. **10**:113, 1952.

203. Basylewycz, I. V.: Pernicious Anemia in Old Age, Rhode Island M. J. **34**:641, 1951.

204. Schwartz, S. O.: Pernicious Anemia in the Negro, Illinois M. J. **100**:110, 1951. Trowell, H. C.: Pernicious Anaemia and Macrocytic Anaemia in Africans in Uganda, Lancet **2**: 761, 1951.

205. Meyer, L. M., and Bertcher, R.: Blood Volume Studies in Pernicious Anemia and Non-Tropical Sprue, Proc. Soc. Exper. Biol. & Med. **81**:511, 1952.

206. Galt, J.; Hunter, R. B.; Hill, J. M.: Pernicious Anemia Superseded by Polycythemia Vera: Report of a Case, Am. J. M. Sc. **223**:61, 1952.

207. Zaino, E. C., and Choy, D. S. J.: A Fatal Case of Megaloblastic Anemia with Clinical Parkinsonism, New York J. Med. **51**:1637, 1951.

208. Hyland, H. H., and Sharpe, V. J. H.: Optic Nerve Degeneration in Pernicious Anemia, Canad. M. A. J. **67**:660, 1952.

209. Berlin, R.: Addison's Disease: Familial Incidence and Occurrence in Association with Pernicious Anemia, Acta med. scandinav. **144**:1, 1952.

210. (*a*) Colebatch, J. H., and Williams, A. L.: Megaloblastic Anaemia of Infancy, M. J. Australia **2**:121, 1952. (*b*) Baker, S. J., and Sinn, H. J.: Megaloblastic Anaemia of Infancy: Report of a Case, ibid. **1**:750, 1952.

211. Larsen, G.: Red Cell Thickness in Normals and in Pernicious Anemia, Blood **7**:874, 1952.

212. Bertcher, R. W., and Meyer, L. M.: Erythrocyte Potassium Levels in Pernicious Anemia and Non-Tropical Sprue, Proc. Soc. Exper. Biol. & Med. **81**:383, 1952.

213. Davidson.[117d] Footnote 210.

214. (*a*) Harris, J. W.: Vitamin B_{12} Levels in Pernicious Anemia, abstracted, J. Clin. Invest. **31**:637, 1952. (b) Mollin, D. L., and Ross, G. I. M.: The Vitamin B_{12} Concentrations of Serum and Urine of Normals and of Patients with Megaloblastic Anemias and Other Diseases, J. Clin. Path. **5**:129, 1952.

215. Schilling, R. F., and Harris, J. W.: Liver Functions in Untreated Addisonian Pernicious Anemia, J. Lab. & Clin. Med. **40**:718, 1952.

216. DeGowin, E. L.; Hamilton, H. E.; Sheets, R. F.; Janney, C. D., and Ellis, J. A.: The Role of Maturation Arrest in the Low Erythrocyte Counts of Pernicious Anemia, abstracted, J. Lab. & Clin. Med. **40**:790, 1952.

Megaloblasts are scarce in the bone marrows of some patients with pernicious anemia prior to treatment. Intermediate erythroblasts signify a megaloblastic anemia.[217] The bone marrows in two patients with associated infections had extensive myelocytic proliferations with a scarcity of megaloblasts.[218] Inconsistent abnormal liver function tests were noted in 20 patients.[215] In a review of so-called childhood pernicious anemia it was claimed that intrinsic factor deficiency could exist without achlorhydria.[202b] Also, spinal cord dorsal-lateral sclerosis may be present.[219] Bone marrow and gastric hydrochloric acid studies are recommended as the means of separating pernicious anemia from other types of megaloblastic anemia.[220] Two methods have been suggested of indirectly judging gastric secretion, by plasma pepsinogen [221] and by urorennin excretion.[222]

When adequate treatment is not given, death ensues within three years in almost all patients with pernicious anemia. Single spontaneous temporary remissions occur in 85% of the cases.[215]

The reported incidence of malignant and premalignant gastric lesions in pernicious anemia varies from 0.16% to 15.0%. Norcross and co-workers [223] reported a 1.7% incidence in their series, and they questioned the value of periodic roentgenologic study of all patients with pernicious anemia. This report should stimulate interest in complicating carcinoma; in the meantime, it is still the physician's responsibility to filter out the rare resectable asymptomatic gastric carcinoma.

Gastrointestinal disease and surgery in anemia have been extensively reviewed.[117k]

Occult idiopathic steatorrhea was found in four patients with previous diagnoses of pernicious anemia. Failure of liver therapy led to investigation of the stool fat content.[202a] Idiopathic steatorrhea is characterized by macrocytic anemia, histamine-fast achlorhydria, megaloblastic bone marrow, flat glucose tolerance curves, and liquid stools high in fatty acid.[205]

Nutritional macrocytic anemia is associated with an absence of cord changes, free hydrochloric acid in gastric juice, and a younger age incidence than that of pernicious anemia.[117c]

Megaloblastic anemia of pregnancy is relatively rare,[117e] occurring once for every 100 iron-deficiency anemias. Iron-deficiency and megaloblastic anemias often coexist. The condition is most often discovered in the puerperium. Dyspnea and glossitis are common.[117h] The marrow is dimorphic, and the peripheral red cells microcytic or macrocytic.[117g] The marrow in a patient with a long-standing case of acholuric jaundice changed from normoblastic to megaloblastic during pregnancy.[117d] Diet does not appear to be an etiologic factor. The condition sometimes recurs with

217. Downey, H.: The Megaloblast-Normoblast Problem: A Cytologic Study, J. Lab. & Clin. Med. **39**:837, 1952.

218. Strauss, M. B.; Brokaw, R., and Chapman, C. B.: Leukemoid Bone Marrow in Pernicious Anemia, Am. J. M. Sc. **223**:54, 1952.

219. Reisner, E. H., Jr.; Wolff, J. A.; McKay, R. J., Jr., and Doyle, E. F.: Juvenile Pernicious Anemia, Pediatrics **8**:88, 1951.

220. Davis, L. J., and Brown, A.: The Non-Addisonial Megaloblastic Anaemias, Practitioner **168**:223, 1952.

221. Mirsky, A.; Futterman, P., and Kaplan, S.: Blood Plasma Pepsinogen: The Activity of the Plasma for "Normal" Subjects, Patients with Duodenal Ulcer, and Patients with Pernicious Anemia, J. Lab. & Clin. Med. **40**:188, 1952.

222. Olmstead, E. G., and Hirschboeck, J. S.: A Study of Urorennin Excretion in Patients with Pernicious Anemia, abstracted, J. Lab. & Clin. Med. **40**:926, 1952.

223. Norcross, J. W.; Monroe, S. E., and Griffin, B. G.: The Development of Gastric Carinoma in Pernicious Anemia, Ann. Int. Med. **37**:338, 1952.

subsequent pregnancies, but once it is controlled it is considered corrected for each episode. This complication is not regarded as a contraindication for future pregnancies. When histamine-fast achlorhydria exists, the patient should be followed for a period of two years to exclude pernicious anemia.[117e] The white blood cells vary considerably.[117f] Marrow examinations are frequently necessary for diagnosis.[117h]

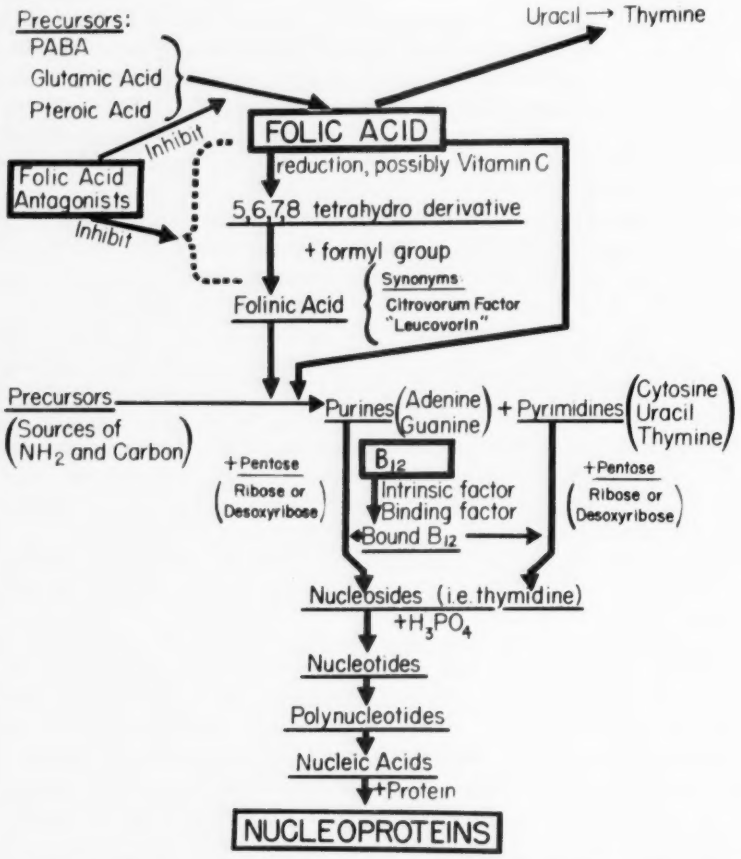

Fig. 1.—A "working outline" for integrating the folic acid-nucleoprotein metabolism. Many phases are hypothetical. There is indirect evidence suggesting that vitamin B_{12} may also be associated earlier in the metabolism than is indicated here.

Megaloblastic anemia of infancy usually occurs prior to the age of 18 months. Celiac disease has been found to be frequently associated with megaloblastic anemias in older children.[224] The clinical phases have been reviewed.[210a] The marrow is indistinguishable from that of adults with pernicious anemia, manifesting abnormalities in all three marrow elements.[210b]

224. Woodruff, C. W., and Peterson, J. C.: The Treatment of Megaloblastic Anemia in Infancy, Postgrad. Med. **10**:189, 1951.

Parasitic macrocytic anemia has been discussed by Birks. In hookworm infestation females develop a megaloblastic anemia and males a microcytic hypochromic anemia. Megaloblastic anemias are also associated with ascariasis infestations.[225]

Etiologic Studies on the Macrocytic Anemias: To facilitate review, the theoretical concepts of folic acid and nucleoprotein metabolism are diagrammed in Figure 1.

Megaloblastic macrocytic anemia has been described as a nucleoprotein metabolic deficiency of the B vitamins,[226] especially B_{12} and folic acid.[227] It may be produced by (1) inadequate diet, (2) gastrointestinal dysfunction (i.e., achylia, lack of intrinsic factor, loss of binding material, diarrhea, neoplasm, inflammation), (3) increased demands (infection, avitaminosis C), or (4) improper utilization (inhibiting factors, cirrhosis).[228]

Some idea of the breadth of interest in this subject is indicated by the following brief summations: Parasitic megaloblastic anemia in Asiatic Indians responds only briefly if worm treatment is not efficacious.[225] Diphyllobothrium latum causes megaloblastic anemia by increased utilization of vitamin B_{12}.[229] In experimental cirrhosis pregnant rats with live fetuses have fewer macrocytic erythrocyte changes than those with dead fetuses.[230] A macrocytic anemia that responds only to folic acid and aureomycin has been produced in rats by the stagnation of intestinal contents within a cul-de-sac.[231] Escherichia coli absorbs more vitamin B_{12} than is necessary for its metabolism.[232]

Role of Folic Acid. In a group of patients with pernicious anemia subacute combined degeneration without anemia developed. They had received multivitamin preparations containing folic acid.[233]

The role of folic acid in nucleoprotein metabolism has been studied indirectly by replacing folic acid with its antagonists.[234] Folic acid replaces *p*-aminobenzoate as a growth factor.[235] Its stimulation of nucleic acid formation involves vitamin

225. Birks, P. H.: Megaloblastic Anemia in Indians, correspondence, Brit. M. J. **1**:764, 1952.

226. (*a*) The Monkey Antianemia Factor, Nutrition Rev. **10**:144, 1952. (*b*) The Role of Folic Acid in Normal Cellular Metabolism, Lederle Bull. **17**:39, 1952.

227. (*a*) Girdwood, R. H.: The Interrelationships of Factors that Influence the Megaloblastic Anemias: Analytical Review, Blood **7**:77, 1952; (*b*) The Relationships Between Vitamin B_{12}, Folic Acid and Folinic Acid, Brit. J. Nutrition **6**:315, 1952. (*c*) Zur Atiologie und Pathogenese der Perniziosa, Deutsche med. Wchnschr. **77**:55, 1952.

228. (*a*) Ungley, C. C.: The Pathogenesis of Megaloblastic Anaemias and the Value of Vitamin B_{12}, Brit. J. Nutrition **6**:209, 1952. (*b*) Colebatch and Williams.[210a]

229. Nyberg, W.: Microbiological Investigations on Antipernicious Anemia Factors in the Fish Tapeworm, Acta med. scandinav., Supp. 271, p. 7, 1952.

230. Goldberg, L.; Hammarsten, G.; Lindgren, G., and Plum, C. M.: Effect of Pregnancy on Macrocytic Anemia in Experimentally Produced Liver Fibrosis, Arch. internat. pharmacodyn. **90**:292, 1951.

231. Watson, G. M., and Witts, L. J.: Intestinal Macrocytic Anemia, Brit. M. J. **1**:13, 1952.

232. Oginsky, E. L.: Uptake of Vitamin B_{12} by Escherichia coli, Arch. Biochem. **36**:71, 1952.

233. Conley, C. L., and Krevans, J. R.: Development of Neurologic Manifestations of Pernicious Anemia During Multivitamin Therapy, New England J. Med. **245**:529, 1951.

234. Recent Developments in Understanding the Role of Folic Acid in Relation to Fundamental Nutritional Problems, Lederle Bull. **16**:47, 1951.

235. Lascelles, J., and Woods, D. D.: The Synthesis of "Folic Acid" by Bacterium Coli and Staphylococcus Aureus and Its Inhibition by Sulphonamides, Brit. J. Exper. Path. **33**:288, 1952.

B_{12} [236] and is thought to deplete B_{12} reserves in patients with pernicious anemia by mass action effect.[236a] Folic acid deficiency decreases choline, cysteine, and glycine production.[236b]

Several studies have been made of the relation of folic acid to folinic acid. A conjugase in an extract of hog kidney liberates the citrovorum factor from its bound form in yeast and chick livers. This enzyme is also present in chick livers and is stimulated by vitamin C.[237] Citrovorum factor is oxidized to a folic-acid-like compound in the stomach of patients with pernicious anemia.[238] In the body folic acid is converted to folinic acid.[227b] Parenteral injection of folinic acid is more active hemopoietically than oral administration,[239] even more so than is the case with folic acid.[240] The toxic effect of folic acid antagonists (especially aminopterin) is not neutralized by folic acid, but folinic acid reverses their effects, indicating that it is a product of folic acid metabolism.[241] Two steps have been postulated by which folinic acid is produced from folic acid: (1) reduction of folic acid to a 5,6,7,8-tetrahydro derivative, a reaction mediated by ascorbic acid (vitamin C), and (2) introduction of a formyl group to produce folinic acid.[226b] Urinary excretion of folic acid compounds indicates that patients with pernicious anemia are defective in the conversion of folic acid to folinic acid.[242] Another growth factor for Leuconostoc citrovorum, different from folinic acid and derived from folic acid, has been designated hemofolin.[243]

Acceleration by ascorbic acid of the conversion of folic acid to folinic acid has been measured by citrovorum factor excretion [244] and ascorbic acid levels in plasma.[245] Ascorbic acid also influences its utilization.[244b] Conversion of folic acid to folinic acid is less efficient in scurvy. Folic acid deficiency in scurvy is apparently

236. Girdwood.[227a] Footnote 234.

236a. Footnote *226 b.* Ungley.[228a]

236b. Stekol, J. A.; Weiss, S., and Weiss, K. W.: Vitamin B_{12} and Folic Acid in the Synthesis of Choline in the Rat, Arch. Biochem. **36**:5, 1952. Footnote *226 b.* Footnote 234.

237. Citrovorum Factor Conjugate, Nutrition Rev. **10**:283, 1952.

238. Hausmann, K., and Mulli, K.: Untersuchungen über den Stoffwechsel der Folsäure und des Citrovorum-Factors, Acta haemat. **7**:1, 1952.

239. Briggs, G. M.; Spivey, M. R.; Keresztesy, J. C., and Silverman, M.: Activity of Citrovorum Factor for the Chick, Proc. Soc. Exper. Biol. & Med. **81**:113, 1952.

240. Sundberg, R. D.; Schaar, F., and May, C. D.: Experimental Nutritional Megaloblastic Anemia: II. Hematology, Blood **7**:1143, 1952.

241. Zink, A.: Folsäure, ihre Antagonisten, B_{12} und Animal Protein Factor und ihre Bedeutung für den tierischen und menschlichen Organismus, Internat. Ztschr. Vitaminforsch. **23**:471, 1952.

242. Spray, G. H., and Witts, L. J.: Conversion of Folic Acid to the Citrovorum Factor in Health and Pernicious Anaemia, Brit. M. J. **2**:62, 1952.

243. Swendseid, M. E.; Wright, P. D., and Bethel, F. H.: A Growth Factor for L. Citrovorum Synthesized by Hemopoietic Tissue Reversing Aminopterin and Chloromycetin Inhibition, Proc. Soc. Exper. Biol. & Med. **81**:689, 1952.

244. (*a*) Gabuzda, G. J., Jr.; Phillips, G. B.; Schilling, R. F., and Davidson, C. S.: Metabolism of Pteroylglutamic Acid and the Citrovorum Factor in Patients with Scurvy, J. Clin. Invest. **31**:756, 1952. (*b*) Ascorbic Acid and the Conversion of Pteroylglutamic Acid to Citrovorum Factor, Nutrition Rev. **10**:40, 1952.

245. Wallerstein, R. O.; Harris, J. W., and Gabuzda, G. J., Jr.: Ascorbic Acid Deficiency in Pernicious Anemia, Proceedings American Federation Clinical Research, National Meeting, Atlantic City, N. J., May 4, 1952.

due to increased folic acid requirements. Only folic acid deficiency produces megaloblastic anemia in scorbutic monkeys.[246] This anemia responds to either folic acid or ascorbic acid but not to vitamin B_{12}.[246] Folic acid prevents the megaloblastosis, but not the normoblastic anemias, of scurvy itself. A specific function for ascorbic acid in hemopoiesis has not been demonstrated.[247]

Role of vitamin B_{12} (cyanocobalamin). The multiple functions of vitamin B_{12} include metabolism of high levels of dietary protein and formation of purine and pyrimidinedeoxyribosides.[226b]

Vitamin B_{12} was first described, in 1948, as a dark red cobalt-containing crystal with a molecular weight of 1,550 to 1,750, having in its molecule three atoms of phosphorus and some nitrogen but no sulfur. Further identification showed that 1,2-dimethyl-4,5-diaminobenzene was a part of the dimethylbenzimidazole riboside.[248] Woodley's amino and nitrophenol substitutions on dimethyldiaminobenzene (similar to a part of vitamin B_{12}) actively inhibit the biosynthesis of vitamin B_{12}.[248b] The reaction product from a strong acid solution of vitamin B_{12} with H_2O_2 exhibits a competitive antagonism to vitamin B_{12}.[249] However, others disagree.[250] Folic acid and vitamin B_{12} are involved in the synthetic glycine-serine-choline progression.

A therapeutic response in a refractory macrocytic anemia has been produced by vitamin B_{12} bound with a factor in normal plasma, from which it is inferred that the patient was deficient in the "binding factor."[251] Vitamin B_{12} injected directly into the marrow produces a response only at the site of injection.[252] With normal serum as a component of the media, fewer megaloblasts are present in erythroblast tissue cultures than when serum from patients with pernicious anemia is used.[253] This ties in with the pernicious-anemia-serum-inhibiting factor of Osgood and co-workers (1937) and Laytha (1950). A heat-stable vitamin-B_{12}-active conjugate has been found in liver.[254]

The lack of vitamin B_{12} has been suggested as the most important cause of symptoms in cobalt-deficient sheep. Their blood and liver storage of vitamin B_{12} is

246. May, C. D.; Hamilton, A., and Stewart, C. T.: Experimental Megaloblastic Anemia and Scurvy in the Monkey: IV. Vitamin B_{12} and Folic Acid Compounds in the Diet, Liver, Urine and Feces and the Effects of Therapy, Blood **7**:978, 1952.

247. Proehl, E. C., and May, C. D.: Experimental Nutritional Megaloblastic Anemia and Scurvy in the Monkey: III. Protoporphyrin, Coproporphyrin, Urobilinogen and Iron in Blood and Excreta, Blood **7**:671, 1952.

248. (*a*) Rivas, F. D.; Suarez, R. M.; Morales, F. H., and Santiago, E. P.: Oral Administration of Vitamin B_{12} in Tropical Sprue, Ann. Int. Med. **36**:583, 1952. (*b*) Vitamin B_{12} Antagonists, Nutrition Rev. **10**:51, 1952.

249. Beiler, J. M.; Moss, J. N., and Martin, G. J.: Formation of a Competitive Antagonist of Vitamin B_{12} by Oxidation, Science **114**:122, 1951.

250. Villela, G. G., and Abreu, L. A.: Lack of Inhibition of Growth of Euglena Bracilis by Vitamin B_{12} Oxidation Product, Science **115**:205, 1952.

251. Horrigan, D. L., and Heinle, R. W.: Refractory Macrocytic Anemia with Defect in Vitamin B_{12} Binding and with Response to Normal Plasma, J. Lab. & Clin. Med. **40**:811, 1952.

252. Horrigan, D. L., and Heinle, R. W.: Role of Tissue Binding in Local Erythroid Maturation Following Instillation of Vitamin B_{12} into Marrow Cavity, abstracted, J. Clin. Invest. **31**:639, 1952. Footnote 251.

253. Feinmann, E. L.; Sharp, J., and Wilkinson, J. F.: Observations on the Behavior of Erythroblasts Cultured in Normal and "Pernicious Anemia" Sera, Brit. M. J. **2**:14, 1952.

254. Hausemann, K., and Mulli, K.: Über die blutbildende Wirkung von Vitamin B_{12} und Vitamin B_{12} Peptidkonjugaten aus Säugetierleber, Acta haemat. **8**:345, 1952.

poor.[255] The cobalt-deficient diet in lambs results in cessation of growth.[256] Anemia in rabbits produced by phenylhydrazine oleate responds better to liver preparations containing cobalt than to cobalt alone.[257] Cobalt-deficient rats have been supplied with sufficient vitamin B_{12} to maintain pregnancy and lactation. However this amount is not enough for normal growth of the offspring.[258] Subcutaneous injection of cobalt nitrate prevents the anemia usually seen following hypophysectomy in rats; vitamin B_{12} and liver extract are ineffective.[259]

Besides stimulating protein and nucleic acid synthesis,[260] a catalytic effect of vitamin B_{12} in transforming folic acid to folinic acid was suggested but not shown experimentally.[226b] Mueller and co-workers[1171] treated three patients with pernicious anemia with folic acid and vitamin B_{12} and noted that thymine increased more rapidly than uracil in the bone marrow. Vitamin B_{12} deficiency reduced the rate of nucleic acid synthesis and thus reduced the rate of cell division. The uptake of N^{15}-labeled glycine in the purines of ribose nucleic acid is lower in vitamin-B_{12}-deficient rats.[261] Nitrogen and phosphorus metabolism was correlated with retriculocyte response to vitamin B_{12} in a patient with pernicious anemia in relapse. Positive nitrogen balance occurred during remission, but blood protein formation was greater than the exogenous source, thus indicating conversion of tissue nitrogen to blood protein. A urinary phosphorus decrease was the earliest biochemical alteration following vitamin B_{12} therapy, but with the appearance of reticulocytes the phosphorus balance became negative while the nitrogen balance was still positive. Uric acid excretion also increased with reticulocytosis.[262]

The megaloblastic bone marrow appears to result from the slowing of maturation.[263] Although megaloblasts disappear at once with specific treatment, cellular nuclei acid (especially ribose nucleic acid) decreases in 3 to 30 days.[264]

Only folic acid causes maturation of megaloblastic cultures of the pernicious anemia marrow in relapse.[265] Chickens, unlike pigs, rats, foxes, or minks, are able

255. Hoekstra, W. G.; Pope, A. L., and Phillips, P. H.: Synthesis of Certain B-Vitamins in the Cobalt Deficient Sheep, with Special Reference to Vitamin B_{12}, J. Nutrition **48**:421, 1952; Response of Cobalt-Deficient Sheep to Intravenously Administered Vitamin B_{12}, ibid. **48**:431, 1952.

256. Cobalt Deficiency in Lambs, Nutrition Rev. **10**:177, 1952.

257. Erdos, J.: Leber- sowie Kobalt-Leberpräparate und Phenylhydrazinanämie, Internat. Ztschr. Vitaminforsch. **23**:494, 1952.

258. Cobalt in Rats, Nutrition Rev. **10**:238, 1952.

259. Crafts, R. C.: The Effects of Cobalt, Liver Extract and Vitamin B_{12} on the Anemia Induced by Hypophysectomy in Adult Female Rats, Blood **7**:863, 1952.

260. Sahasrabudhe, M. R., and Lakshminarayan Rao, M. V.: Effect of Vitamin B_{12} on the Synthesis of Protein and Nucleic Acids in the Liver, Nature, London **168**:605, 1951.

261. Rose, I. A., and Schweigert, B. S.: Effect of Vitamin B_{12} on Nucleic Acid Metabolism of the Rat, Proc. Soc. Exper. Biol. & Med. **79**:541, 1952.

262. James, G. W., III, and Abbott, L. D., Jr.: Metabolic Studies in Pernicious Anemia: I. Nitrogen and Phosphorus Metabolism During Vitamin B_{12}-Induced Remission, Metabolism **1**:259, 1952.

263. (*a*) Sturgis, C. C.: Etiology and Treatment of Pernicious Anemia, Postgrad. Med. **2**:83, 1952. (*b*) Scott and Govan.[117g]

264. Menten, M. L., and Willms, M.: Nucleic Acid in Cells of Bone Marrow of Patients with Pernicious Anemia, A. M. A. Arch. Path. **54**:351, 1952.

265. Thompson, R. B.: Observations on the Effects of Vitamin B_{12}, Liver Extracts, Folic Acid and Thymine on the Maturation of Megaloblasts in Culture, Blood **7**:522, 1952.

to maintain normal hematocrit and hemoglobin levels in vitamin B_{12} deficiency, but their growth is retarded.[266] The experimental production of macrocytic anemia in vitamin-B_{12}-deficient pigs has not been confirmed.[267] Methods of measuring vitamin B_{12} folic acid, and folinic acid in whole blood of rats, chicks, oxen and sheep were described by Pfander and co-workers.[268]

Role of intrinsic factor. Intrinsic factor production occurs largely in the fundus; the argentaffin cells do not secrete it.[269] The glandular mucoprotein fraction of the gastric "dissolved mucin" is considered the main carrier of the intrinsic factor activity of human gastric juice.[270] Intrinsic factor activity is found in the muscularis as well as in the mucosa of the pig's pylorus.[271] Vitamin B_{12} is not potentiated by intrinsic factor if the mixture is given parenterally.[272] Lysozyme has been found to have no intrinsic factor effect.[273] The vitamin B_{12} "binding factor" in gastric juice combines with vitamin B_{12} and thus prevents its utilization by micro-organisms. This "binding factor" is not identical with the intrinsic factor [274] and has no relation to the plasma "binding factor" for body utilization.

Treatment of the macrocytic anemias: Pernicious anemia. Many authors have discussed past and present concepts of pernicious anemia therapy.[275] Hematologic

266. (*a*) Cartwright, G. E.; Tatting, B.; Kurth, D., and Wintrobe, M. M.: Experimental Production of Nutritional Macrocytic Anemia in Swine: V. Hematologic Manifestations of a Combined Deficiency of Vitamin B_{12} and Pteroylglutamic Acid, Blood **7**:992, 1952. (*b*) Stern, J. R.; Hsu, J. N., and McGinnis, J.: Vitamin B_{12} and Hemoglobin Regeneration in the Chick, J. Biol. Chem. **194**:191, 1952.

267. Vitamin B_{12} Deficiency in Swine, Nutrition Rev. **10**:104, 1952.

268. Pfander, W. H.; Dietrich, L. S.; Monson, W. J.; Harper, A. E., and Elvehjem, C. A.: Citrovorum Factor, Vitamin B_{12}, and Folic Acid Activity of Whole Blood of Several Species, Proc. Soc. Exper. Biol. & Med. **79**:219, 1952.

269. Landboe-Christensen, E.: Argentaffin Cells and Pernicious Anemia, Am. J. M. Sc. **223**:182, 1952. Landboe-Christensen, E.; Berk, L., and Castle, W. B.: Observations on the Etiologic Relationship of Achylia Gastrica to Pernicious Anemia: XIV. Intrinsic Factor Activity of Desiccated and Defatted Human Fundus, Duodenum, and Jejunum, ibid. **224**:1, 1952.

270. Glass, G. B. J.; Boyd, L. J.; Rubinstein, M. A., and Svigals, C. S.: Relationship of Glandular Mucoprotein from Human Gastric Juice to Castle's Intrinsic Antianemic Factor, Science **115**:101, 1952.

271. Meulengracht, E.: Further Investigations into the Localization of the Antianemic Factor (Intrinsic Factor) in the Stomach: VII. The Antianemic Activity of the Pyloric Mucosa and the Pyloric Muscularis, Respectively, of the Pig's Stomach, Acta med. scandinav. **143**:207, 1952.

272. Wallerstein, R. O.; Harris, J. W., and Schilling, R. F.: Effects of Oral and Intravenous Gastric Juice upon Vitamin B_{12} Activity in Pernicious Anemia, abstracted, J. Clin. Invest. **31**:669, 1952.

273. Hoff-Jorgensen, E.: The Effect of "Intrinsic Factor" on the Absorption of Vitamin B_{12} by Wild Type Escherichia Coli, Arch. Biochem. **36**:235, 1952.

274. Spray, G. H.: The Effect of Heat on the Microbiological and Anti-Anemic Properties of Human Gastric Juice mixed with Vitamin B_{12}, Biochem. J. **50**:587, 1952.

275. (*a*) Murphy, W. P.: Twenty-Five Years' Experience in Treatment and Management of Pernicious Anemia, J. A. M. A. **149**:907, 1952. (*b*) Welch, A. D., and Heinle, R. W.: Hematopoietic Agents in Macrocytic Anemia, Pharmacol. Rev. **3**:346, 1951. (*c*) The Antianemic Factors Concerned in Macrocytic Anemias, editorial, Ann. Int. Med. **36**:1351, 1952. (*d*) Treatment of Pernicious Anemia, editorial, Brit. M. J. **2**:659, 1952. (*e*) Blackburn, E. K.; Burke, J.; Roseman, C., and Wayne, E. J.: Comparison of Liver Extract and Vitamin B_{12} (Cyanocobalamin) in Maintenance Treatment of Pernicious Anaemia, Brit. M. J. **2**:245, 1952. (*f*) Conley, C. L.; Green, T. W.; Hartmann, R. C., and Krevans, J. R.: Prolonged Treatment of Pernicious Anemia with Vitamin B_{12}, Am. J. Med. **13**:284, 1952. (*g*) Sturgis.[265a]

remissions were produced with liver therapy in 60 of 63 patients studied from 1 to 20 years.[276] Failure occurs in patients with other complicating diseases. Neurologic improvement results from large doses of liver. Good results in prolonged vitamin B_{12} therapy have been reviewed.[275f] Variable responses have been noted to oral administration of vitamin B_{12} alone. Marked potentiation results when normal gastric juice is added.[219] Oral requirements of vitamin B_{12} are 100 times the parenteral requirements.[275f] Single, massive (1 mg.) intramuscular doses of vitamin B_{12} proved to be impractical.[277] Relapses and neurologic deterioration have been noted six weeks to one year after treatment. The dosage requirements of vitamin B_{12} vary widely.[275d] A schedule of 10 γ intramuscularly per day for initial treatment is recommended.[275c] Maintenance schedules vary from 45 γ intramuscularly every six weeks[275f] to 50 γ intramuscularly every two weeks.[117e] There is general agreement that vitamin B_{12} is therapeutically equal to liver.[278] It has been suggested that there is an inequality between 1 U. S. P. unit of liver and 1 γ of vitamin B_{12}.[275a] Neurologic improvements have also been obtained with high doses of vitamin B_{12}.[279] Therapy with vitamin B_{12} is preferred to liver injections because of economy, better standardization, and less painful injections. Inadequate dosage is the cause of some of the vitamin B_{12} failures.[280] A synergistic enhancement of suboptimal oral doses of vitamin B_{12} and folic acid has been attributed to minute amounts of vitamin B_{12} absorbed even in intrinsic factor deficiencies.[281] Folic acid is not recommended for treating pernicious anemia.[282] Such therapy is comparable to prescribing a single vitamin for a multiple deficiency. It is not a necessary adjuvant when diets are adequate; however, it is not harmful in the presence of adequate amounts of vitamin B_{12}.[266b] Good clinical and hematologic responses have been obtained with citrovorum factor.[283] Remission of neurologic manifestations occurs following 10 mg. daily oral doses,[284] but a 6 mg. daily oral dosage schedule was ineffective in one patient.[283a]

Marrow changes can be detected two and one half hours after intramuscular injections of vitamin B_{12}.[285] Downey[217] dealed the marrow alterations before and

276. Cameron, D. G.; Townsend, S. R., and Mills, E. S.: Pernicious Anaemia: I. Maintenance Treatment with Liver Extract, Canad. M. A. J. **65**:241, 1951.

277. Walker, W., and Hunter, R. B.: Single Massive Dose of Vitamin B_{12} in Untreated Pernicious Anaemia, Brit. M. J. **2**:593, 1952.

278. Murphy, W. P., and Howard, I.: A Comparison of the Effect of Vitamin B_{12} with that of Liver Extract in the Treatment of Pernicious Anemia During Relapse and for Maintenance, New England J. Med. **247**:838, 1952. Footnote 117*e*. Footnote 275*c*, *d*, and *e*.

279. Gelin, C.; Coirault, R., and Bab-Hamed, E. H.: Vitamine B_{12} et syndromes neuro-anémique, Ann. méd. lég. **53**:172, 1952.

280. Footnote 117*e*. Footnote 275*e* and *f*.

281. Reisner, E. H., and Weiner, L.: Studies on the Mutual Effect of Suboptimal Oral Doses of Vitamin B_{12} and Folic Acid in Pernicious Anemia, New England J. Med. **247**:15, 1952.

282. Cohen, Meyer, and Fadem.[117j] Footnote 275*c*. Reisner and Weiner.[281]

283. (*a*) Meyer, L. M., and Diefenbach, W. C. L.: Pernicious Anemia Treated with Citrovorum Factor (Leucovorum), Am. J. Clin. Path. **21**:1054, 1951. (*b*) Davidson, L. S. P., and Girdwood, R. H.: Treatment of the Megaloblastic Anaemias with Citrovorum Factor, Lancet **2**:1193, 1951.

284. Moore, N. S.; Scott, M. L.; Wallace, C. S., and Fiala, G.: Orally Administered Citrovorum Factor in the Treatment of Pernicious Anemia with Neurologic Complications, New York J. Med. **51**:2645, 1951.

285. Etess, A. D., and Litwins, J.: Pernicious Anemia with Early Marrow Change Following Therapy, New York J. Med. **51**:2787, 1951.

during therapy. The marrow of pernicious anemia in relapse is not always pathognomonic.[218] There has been no change found in blood volumes after remission.[205] This is attributed to concurrent loss of blood plasma and a gain in red cell mass. Patient education is also stressed as an important part of therapy.[286]

The physician's major responsibilities to the patient with pernicious anemia are (1) the arresting or prevention of combined system disease and (2) the discovery of the rare resectable gastric carcinoma. The anemia is reversible, but these complications may not be.

Macrocytic anemia following gastrointestinal surgery. This condition generally responds to folic acid therapy. When neurologic symptoms develop, vitamin B_{12} or liver is required. Occasionally the initial anemia does not respond to vitamin B_{12} but does respond when folic acid is added.[117k]

Sprue. The hematologic and clinical abnormalities of sprue are alleviated by either vitamin B_{12} or folic acid therapy but not by oral or sublingual vitamin B_{12}.[287] Initial vitamin B_{12} intramuscular doses recommended are 100 γ,[287a] followed by 15 γ daily.[284a] Maintenance therapy is adequate with 15 γ weekly. In one case cited the patient was refractory to large intramuscular doses of vitamin B_{12} but responded to folic acid.[117j] Oral doses of 10 to 15 mg. of folic acid daily are generally necessary. Both folic acid and vitamin B_{12} are thought necessary in sprue.[288] Thymine is effective in doses 5,000 times greater than folic acid.[117j] Satisfactory clinical and hematologic responses were obtained in six patients treated with 1,000 units of folinic acid (citrovorum factor, Leucovorin) given intramuscularly daily for 12 days. No untoward effects were noted. Folinic acid on a weight basis was judged to be 10 to 15 times more effective than folic acid.[289] The marrow changes have been discussed by Downey.[217] A decrease in blood volume was noted in one patient after therapy.[205]

Idiopathic steatorrhea. Four patients with idiopathic steatorrhea had variable suboptimal responses to liver therapy but responded well to folic acid.[202a] One hundred milligrams of cortisone daily for four weeks failed to improve the steatorrhea in four patients; however, there was subjective improvement.[290] Some response was noted in one patient treated with citrovorum factor.[283b]

Nutritional macrocytic anemias. These anemias respond to folic acid.[117j,k]

Pregnancy. Folic acid is effective in megaloblastic anemia of pregnancy.[291] An oral dose of 20 mg. daily is given until the blood count has been normal for one month.[117h,l] Severely anemic patients and those near term receive 30 mg. intramuscularly daily or 100 mg. intravenously in 250 ml. of isotonic sodium chloride solution.[117h] Iron supplements are used to correct the frequently associated iron

286. Todd, J. W.: Suffering from Pernicious Anemia, Lancet, **2**:1227, 1952.

287. (*a*) Suarez, R. M.: The Comparative Effect of Vitamin B_{12} Administered Through Different Routes in Tropical Sprue, Internat. Rev. Vitamin Res. **23**:308, 1952. (*b*) Rivas, F. D.; Morales, F. H., and Meyer, L. M.: The Oral Use of Combined Vitamin B_{12} and Folic Acid in Tropical Sprue, Ann. Int. Med. **36**:1076, 1952. (*c*) Suarez, R. M.; Sabater, J.; Suarez, R. M., Jr., and Buso, R.: The Effect of Sublingual Administration of Crystalline Vitamin B_{12} in Tropical Sprue, Blood **7**:749, 1952. (*d*) Footnote 117*k*. (*e*) Rivas and others.[248a]

288. Rivas and others.[248a] Rivas, Morales, and Meyer.[287b]

289. Romero, C. A.; Vizcarrondo, R., and Rodriguez-Molina, R.: Treatment of Sprue with Folinic Acid, Am. J. M. Sc. **224**:9, 1952.

290. Badenoch, J.: Cortisone in Idiopathic Steatorrhea, Brit. M. J. **1**:356, 1952.

291. Footnote 117*a*, *b*, *c*, *g*, *j*, and *k*.

deficiency anemias,[292] however, iron alone is unsatisfactory. Vitamin B_{12} is generally ineffective [117b,e] although it was effective in one case.[117i] The anemia is preventable when diets are rich in folic acid (greens, liver, yeast) or folic acid supplements.[293] Success has also been obtained with citrovorum factor.[117d]

Infancy. Permanent remissions follow the use of folic acid in the megaloblastic anemia of infancy.[294] Response is dramatic and usually occurs within two weeks.[295] A lasting remission has been obtained with a single 15 mg. dose.[210b] Doses recommended are 5 mg. orally every day for two weeks or 5 to 15 mg. parenterally every day if gastrointestinal disturbances are present.[224] In rare instances relapse occurs when liver therapy is stopped.[296]

Since the anemia is hastened by vitamin C deficiencies, prophylactic vitamin C is recommended.[297] Transfusions are necessary only in patients with extreme anemia or serious complicating infections. Iron is necessary for prevention of the hypochromic anemia resulting from the rapid growth which usually follows recovery.[224]

Pharmacology. 1. Vitamin B_{12}. Several editorials emphasize the proper use of vitamin B_{12} and other antianemic substances. Specific diagnosis prior to instituting specific treatment is stressed.[298]

Vitamin B_{12} content in fresh soft- and hard-shelled clams is higher than in calf, pig, or beef liver.[299] An excellent clinical remission has been obtained with a vitamin-B_{12}-like product made from fish.[300] Smith [301] has reviewed the methods for chemical and biologic assay of vitamin B_{12}.

Absorption of orally administered vitamin B_{12} varies.[302] Urinary excretion of vitamin B_{12} is the same for normal persons and untreated patients with pernicious anemia. Excretion studies with varying doses of vitamin B_{12} indicate that the body can become saturated.[303] Patients with pernicious anemia showed a rise in blood and marrow levels directly proportional to the dose of vitamin B_{12}.[304] Skin sensitivities

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292. Footnote 117*c*, *g*, and *h*.

293. Folic Acid Deficiency in Macrocytic Anemia of Pregnancy and Infancy, editorial, J. A. M. A. **148**:1422, 1952.

294. Rickards, A. G.: Megaloblastic Anemia of Infancy, Brit. M. J. **1**:1226, 1952. Footnote 117*k*, Baker and Sinn.[210b] Woodruff and Peterson.[224]

295. Baker and Sinn.[210b] Woodruff and Peterson.[224]

296. Najman, E., and Brausil, E.: Megaloplastische Anämie mit Relapsen ohne Achylia gastrica im Kindesalter, Ann. pædiat. **178**:47, 1952.

297. Castle, W. B.; Elvehjem, C. A.; May, C. D.; Welch, A. D.; Zuelzer, W. W., and Butler, A. M.: Vitamin B_{12} and Folic Acid in Infant Nutrition, J. A. M. A. **146**:1028, 1951. Footnote 117*a*. Woodruff and Peterson.[224] Footnote 293.

298. Heck, F. J.: Proper Use of Iron, Liver Extract, Vitamin B_{12}, and Folic Acid in Anemias, J. A. M. A. **148**:783, 1952. Footnote 117*c*. Etess and Litwins.[285]

299. Proctor, B. E., and Lang, D. A.: Vitamin B_{12} Content of Soft and Hard-Shell Clams, Nature, London, **168**:36, 1951.

300. Haufmann, K., and Mulli, K.: The Haemopoietic Effect of Vitamin B_{12} Prepared from Fish, Lancet **1**:185, 1952.

301. Smith, E. L.: Vitamin B_{12}: The Discovery and Identification of Vitamin B_{12}, Brit. J. Nutrition **6**:295, 1952.

302. The Utilization of Vitamin B_{12}, Nutrition Rev. **10**:219, 1952.

303. Sokoloff, M. F.; Sanneman, E. H., Jr., and Beard, M. F.: Urinary Excretion of Vitamin B_{12}, Blood **7**:243, 1952.

304. Unglaub, W. G., and Rosenthal, H. L.: Studies of Vitamin B_{12} in Human Serum, abstracted, J. Clin. Invest. **31**:667, 1952. Harris.[214a]

and mild side reactions occurring with commercial vitamin B_{12} preparations are attributed to impurities from the mold fermentation liquor.[305] Reactions are twice as frequent in persons having had previous antibiotic therapy. The possibility of inducing sensitivity to antibiotics with impure preparations of vitamin B_{12} made from mold cultures has been suggested.

Effects of vitamin B_{12} on lead porphyrinuria, carbon tetrachloride poisoning, and growth failure problems have been reported.[306] Vitamin B_{12} prevents fatty livers in rats and increased growth response to choline and betaine in chicks.[226b] It has been included also with the large group of anticachetic substances called "animal protein factors."[307]

2. Folic acid. Favorable responses to proteolized liver or folic acid occur in some patients refractory to vitamin B_{12} or concentrated liver extract. Jukes[308] has discussed the chemical nature of folic acid and related substances. The folic acid conjugases in body tissues may break the peptide linkages of naturally occurring folic acid. Increased hemopoietic activity has been found in xanthine-oxidase-treated folic acid.[309]

An extensive outpouring of immature leucocytes follows folic acid therapy in the megaloblastic anemias of pregnancy.[117f] Acute granulocytic leukemia developed in one patient with pernicious anemia who had received liver extract, folic acid, and vitamin B_{12} over several years.[310]

Citrovorum factor is more effective parenterally than orally.[238]

3. Liver. Murphy noted arterial hypertension in 47% of P. A. patients with pernicious anemia treated with liver extract. He thought this was due to age and not to liver therapy.[276]

Iron Metabolism, Iron Deficiency Anemias, and Disturbances in Pigment Metabolism.—Iron: Deficient iron intake. In an excellent study and review of the anemia of infancy, Reedy and co-workers[311] found that anemia in the premature infant varies in direct relation to the birth weight. The untreated infants remain severely anemic until iron therapy is given. Reference to the original article is suggested. Another study, of 2,563 Canadian Indian children under two years of age, shows an 84.5% incidence of iron deficiency anemia, attributed to a lengthened nursing

305. Bedford, P. D.: Side-Effects of a Preparation of Vitamin B_{12}, Brit. M. J. **1**:690, 1952.

306. Frank, O.; Lachnit, V., and Neumayr, A.: Der Einfluss von Vitamin B_{12} auf die Bleiporphyrurie, Acta Haemat. **8**:42, 1952. Prinzie, A.: Effet lipotrope de la vitamin B_{12}, Arch. internat. physiol. **60**:110, 1952. Recovery from Growth Failure with Vitamin B_{12} Supplements, Publication 175, What's New, Abbott's Laboratories, North Chicago, Ill., 1953. Spies, T. D.; Dreizen, S.; Currie, C., and Buehl, C. C.: The Effect of Supplements of Vitamin B_{12} on the Growth of Children with Nutritive Failure, Int. Rev. Vitamin Res. **23**:414, 1952.

307. Barnard, R. D.; Orens, L. R., and Schwartz, M.: A. P. F. in Megaloblastic Anaemia, Brit. M. J. **2**:612, 1952.

308. Jukes, T. H.: Folic Acid, Int. Rev. Vitamin Res. **23**:356, 1952.

309. Jacobson, W., and Good, P. M.: The Haemopoietic Activity of Folic Acid Treated with Xanthine Oxidase, Quart. J. Med. **21**:1, 1952.

310. Talley, R. W.; Doherty, J. E.; Shukers, C. F.: Pernicious Anemia Complicated by Acute Granulocytic Leukemia, South. M. J. **45**:559, 1952.

311. Reedy, M. E.; Schwartz, S. O., and Plattner, E. B.: The Anemia of the Premature Infant, Am. J. Pediat. **41**:25, 1952.

period and delayed introduction of solid food. Iron therapy induced improvement in energy, appetite, and well-being.[312]

Blood donor records of the American Red Cross[313] reveal that 1% of men and 12.6% of women are unable to meet the minimal donor requirement of 12.3 gm. hemoglobin per 100 cc. Disqualifications are most numerous in the childbearing ages. Supplemental iron therapy after donations reduces the percentage of rejections in repeated donors, particularly in women.[188] German reports also emphasize similar findings in repeated donors and recommend protein diet supplements to iron.[314]

Iron transport, utilization, and storage. To facilitate review of the iron metabolism cycle a schematic diagram is presented in Figure 2.

Available evidence supports the theory that the transferrin (iron and beta globulin) in plasma is the carrier of iron and that iron enters and leaves the blood in ionized form.[315] Variations in serum iron are the result of (1) variations in the

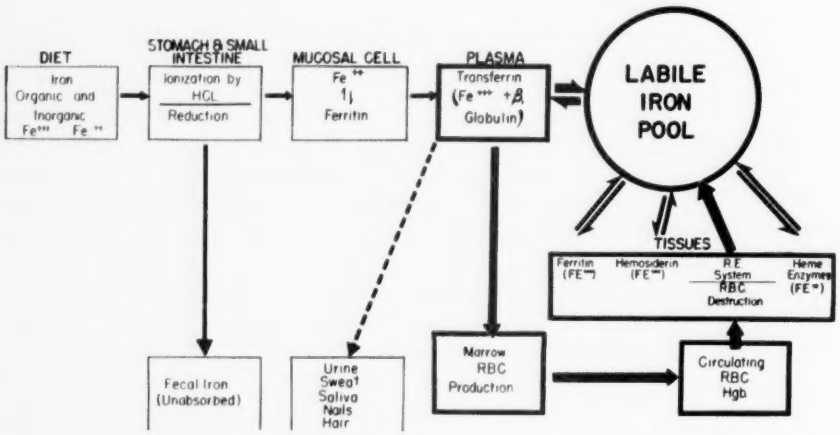

Fig. 2.—An outline of iron metabolism, exclusive of myoglobin (modified after Cartwright, in Wintrobe, M. M.: Clinical Hematology, Ed. 3, Philadelphia, Lea & Febiger, 1951, p. 119).

transferrin level, (2) the available storage iron, (3) the rate of formation and destruction or iron porphyrins, and (4) iron demand. Low serum iron during infections is ascribed to accumulation of iron in the reticuloendothelial system in an unavailable form.[316] This hypoferremia appears to be mediated at least in part by the adrenal

312. Millar, J.: Some Observations on Haemoglobin Levels of an Indian Population, Canad. M. A. J. **67**:414, 1952.

313. Hervey, G. W.; McIntire, R. T., and Watson, V.: Low Hemoglobin Levels in Women as Revealed by Blood Donor Records, J. A. M. A. **149**:1127, 1952.

314. Remy, D.; Goldeck, H., and Krüger, E.: Eisenmangel bei häufigem Blutspenden, Deutsche med. Wchnschr. **77**:1253, 1952.

315. Laurell, C. B.: Plasma Iron and the Transport of Iron in the Organism, Pharmacol. Rev. **4**:371, 1952.

316. Weissbecker, C. K.: Die Infektanämie, ihre Ursache und Behandlung, Deutsche med. Wchnschr. **77**:1452, 1952.

cortex.[317] Protein-depleted rats show diminution in hemoglobulin formation.[318] Both of these phases are associated with the anemia of chronic and/or debilitating diseases. Erythrocyte breakdown has been studied in dogs whose storage iron had been previously labeled. Only 10% of the storage iron is utilized for erythropoiesis.[234]

Hemochromatosis. Hemochromatosis is characterized by skin pigmentation, cirrhosis of the liver, diabetes mellitus, and endocrine hypofunction due to deposition of iron in the form of hemosiderin. Five to ten times the normal amount of iron may be found in the body at autopsy. Deposits of iron probably stimulate the proliferation of fibrous tissue.[319] Multiple transfusions,[320] protein deficiency,[321] low dietary phosphorus (i. e. corn grits diet),[322] and unknown factors [323] have been implicated in the pathogenesis of the disease.

Hemochromatosis may develop gradually or suddenly.[323] The heart involvement has been emphasized.[324] Megaloblastic anemia also may be associated.[325]

The intravenous iron-tolerance test has been suggested as a means of differentiating hemochromatosis from Laennec's cirrhosis. Characteristics of hemochromatosis are (1) a high fasting serum iron level, (2) an extremely high percentage saturation of the total serum-iron-binding capacity, (3) a high decrease/increase ratio, and (4) a flat iron-absorption curve.[326] These tests are superior to skin or liver biopsies.

Repeated phlebotomies are therapeutically beneficial; however, this can be rigorous and is not without danger in the debilitated patient.[327]

Normally the body is tenacious with iron and its storage. Means of disposal of excess parenteral iron are meager outside of hemorrhage or pregnancy. Thus hemochromatosis is rarer in women. The potential danger of its development in excessive parenteral iron therapy has been repeatedly pointed out.[119b]

317. Serum Iron and the Adrenal Cortex, Nutrition Rev. **9**:250, 1951.

318. Bethard, W. F.; Wissler, R. W.; Thompson, J. S., and Robson, M. J.: The Distribution and Utilization of Radio-Iron (Fe^{59}) in Protein Depleted Rats, abstracted, J. Clin. Invest. **31**:617, 1952.

319. Hemochromatosis, editorial, Lancet **2**:650, 1952.

320. Block, M.; Bethard, W., and Jacobson, L.: Secondary Hemochromatosis, J. Lab. & Clin. Med. **40**:781, 1952.

321. Schwietzer, C. H.: Eiweissmangel als ätiologische Moment der Hämochromatose, Deutsche med. Wchnschr. **77**:17, 1952.

322. Species Differences in Iron Absorption, Nutrition Rev. **11**:19, 1953.

323. Doane, J. C.; Krabitz, C. H., and Rosenstein, G.: Hemochromatosis, J. A. M. A. **146**:926, 1951.

324. Bothwell, T. H.; Van Lingen, B.; Alpert, T., and DuPreez, M. L.: Cardiac Complications of Hemochromatosis: Report of a Case Including Radioiron Studies and a Note on Etiology, Am. Heart J. **43**:333, 1952. Swan, W. G. A., and Dewar, H. A.: The Heart in Haemochromatosis, Brit. Heart J. **14**:117, 1952.

325. Koszewski, B. J.: The Occurrence of Megaloblastic Erythropoiesis in Patients with Hemochromatosis, Blood **12**:1182, 1952.

326. Davies, G.; Levin, B., and Oberholzer, V. G.: The Micro Estimation of Serum Iron and Iron-Binding Capacity in Normals and in Disease, J. Clin. Path. **5**:312, 1952. Houston, J. C., and Thompson, R. H. S.: The Diagnostic Value of Serum Iron Studies in Hemochromatosis, Quart. J. Med. **21**:215, 1952. Gitlow, S. E., and Beyers, M. R.: Metabolism of Iron: Intravenous Iron Tolerance Tests in Normal Subjects and Patients with Hemochromatosis, J. Lab. & Clin. Med. **39**:337, 1952. Wasserman and others.[11c]

327. Davis, W. D., and Arrowsmith, W. R.: The Effect of Repeated Phlebotomies in Hemochromatosis, J. Lab. & Clin. Med. **39**:526, 1952.

Excessive iron loss. The source of chronic blood loss may be difficult to demonstrate, but the hypochromic microcytic red blood cell picture is typical. Frequently it is the presenting and only diagnostic clue. Among the many causes are hookworm infestation,[328] diverticuloses (including Meckel's [329]), intestinal malignant conditions, Schönlein-Henoch syndrome, hereditary hemorrhagic telangiectasia, ulcerative colitis, hemorrhoids, hiatus hernia, esophageal varices, scurvy, and others.[330]

Iron therapy. Orally administered iron does not pass freely through the intestinal wall. It is stored temporarily in the mucosal cells of the intestine in the form of ferritin. From here it proceeds into the blood stream according to the need.[331] Iron absorption has been studied by growing foods in the presence of radioactive iron. Radioactive-iron-containing foods were fed to normal and iron-deficient subjects.[332] Rather surprisingly, absorption was the same in both. Absorption is enhanced by ascorbic acid but not by dilute hydrochloric acid.

Tests with orally administered radioactive iron revealed that (1) only 0.2% is utilized by patients with infection, (2) in pregnancy utilization is increased to 26%, (3) iron utilization in malignant and cardiovascular diseases is not abnormal.[333] Anemic patients with iron deficiency incorporate 40 to 62% of administered iron.[334] There are no great quantitative differences in absorption of ferrous gluconate, lactate, and sulfate; however, ferrous lactate is claimed to be more consistently absorbed under certain circumstances.[335] Organic liquid ferrous gluconate with ascorbic acid is claimed to be more effective than the inorganic forms.[336] Effective absorption and minimal gastrointestinal disturbances have been reported in trials with a colloidal iron compound.[337] Ferrous sulfate plus molybdenum oxide tablets have again been claimed to be tolerated better than ferrous sulfate alone in anemias of pregnancy.[119a]

As previously mentioned, most of the iron given intravenously is retained; thus, the danger of excessive iron storage. Toxic reactions to intravenous iron occasionally occur. Oral iron therapy is always preferred if possible. The indications for the intravenous use of iron are (1) uncomplicated anemia caused by deficiency in iron that has been unresponsive to prolonged periods of adequate oral administration, (2) intolerance to oral iron, (3) the rare sensitivity to oral iron, (4) iron deficiency anemia discovered late in pregnancy, and (5) deficiency resulting from severe hemorrhage in patients who refuse transfusions.[119c] Contraindications to intravenous

328. Lehmann, H.: Anemia in Africans in Uganda, Lancet **1**:311, 1952.

329. Walton, J. N., and Lill, N. D.: Bleeding Meckel's Diverticulum, Brit. M. J. **1**:88, 1952.

330. Edwards, E. W.: Anemias of Blood Loss and Iron Deficiency Associated with Gastrointestinal Disease, New York J. Med. **52**:2244, 1952.

331. Wendel, H.: Eisendosierung und Eisenresorption, Deutsche med. Wchnschr. **77**:268, 1952.

332. Moore, C. V.: Absorption of Radio Iron from Food, Science **116**:527, 1952.

333. West, H. D.; Jackson, A. H.; Elliott, R. R.; Hahn, P. F.; Patterson, W. A., and Anderson, R. S.: The Utilization of Ingested Iron in Disease, South. M. J. **45**:629, 1952.

334. Chodos, R. B., and Ross, J. F.: Absorption of Radioactive Iron in Normal, Anemic, and Hemochromatic Subjects, Proceedings, American Federation Clinics Research, National Meeting, Atlantic City, N. J., May 4, 1952.

335. Graham, M. R., and Leverton, R. M.: Iron Absorption by Women: Comparison of 3 Ferrous Salts, J. Lab. & Clin. Med. **39**:871, 1952.

336. Haler, D.: The Therapeutic Response of Secondary Anaemias to Organic and Inorganic Iron Salts, Brit. M. J. **2**:1241, 1952.

337. Fowler, W. N., and Barer, A. P.: Plasma Iron: Normal Values; Response Following Medication, Am. J. Med. Sc. **223**:633, 1952.

therapy are severe idiosyncrasy to iron and severe renal damage.[338] Saccharated iron oxide for intravenous injection is relatively effective and safe. Doses above 200 mg. produce a transient leucopenia, which is attributed to the colloidal component.[339] Other preparations studied are an iron-lecithin preparation [340] and a high molecular weight ferric carbohydrate compound.[341] No intravenous iron is excreted in the feces; up to 4% is excreted in the urine.[342] General experiences with intravenous iron have been reviewed.[343]

Acute iron poisoning in children after the accidental ingestion of ferrous sulfate pills produces nausea, vomiting, hematemesis, and profound shock.[344] Autopsy in two cases revealed necrosis and sloughing of the stomach and duodenal mucosa. Recommended treatment includes induction of vomiting; gastric lavage with sodium bicarbonate, which forms less toxic ferrous carbonate, and intravenous fluids, plasma, or blood. Repeated emphasis is made that medicinal iron can be a poison and should be treated as such in the home.

Special Iron Studies. Serum iron levels in acute hepatitis are elevated and have proved to be a sensitive index of hepatic damage.[345] Plasma iron-copper ratio has been suggested as a means of differentiating hepatitis and occlusion icterus. High serum iron with low copper levels indicates hepatitis.[346] Serum iron is not elevated in extrahepatic obstructive jaundice, cirrhosis, "chronic" hepatitis, or fatty infiltration of the liver.[345a] An interesting correlated study has been made of the morphologic estimations of marrow iron and serum iron.[347] In iron deficiency anemias there

338. Deshmukh, P. L.: Intravenous Iron Therapy with Saccharated Iron Oxide, Indian M. Gaz. **87**:287, 1952.

339. Murphy, R. A.: Experiences with Intravenous Iron in the Treatment of Iron Deficiency Anemia, Univ. Michigan M. Bull. **18**:337, 1952. White, L. P.; Bierman, H. R.; Kelly, K. L., and Byron, R. L., Jr.: The Immediate Hematologic Effects of Intravenous Saccharated Iron Oxide, Blood **7**:897, 1952. Deshmukh.[338]

340. Krebs, A.: Zur Frage der intravenösen Eisentherapie, Deutsche med. Wchnschr. **77**:303, 1952.

341. Lucas, J. E., and Hagedorn, A. B.: The Intravenous Use of High Molecular Ferric Carbohydrate Compound in the Treatment of Hypochromic Anemia, Blood **7**:358, 1952.

342. Crawley, J.: Iron Absorption Tests in Anaemia: The Use of Intravenous Iron Preparations, Edinburgh M. J. **59**:478, 1952.

343. Wiesener, H.: Die Behandlung von Anämien im Säuglings- und Kindesalter mit dreiwertigem Eisen, Deutsche med. Wchnschr. **77**:622, 1952. Feser, A.: Zur Behandlung der Eisenmangelanämien mit hohen introvenösen Eisengaben, ibid. **77**:84, 1952. Bruckmooser, M.: Erythropoese, Mitosenverläufe und klinische Erfahrungen bei Infectänämien unter Behandlung mit Ferriamphiolen, ibid. **77**:301, 1952.

344. Duffy, T. L., and Diehl, A. M.: Ferrous Sulphate Poisoning, J. Pediat. **40**:1, 1952. Acute Iron Poisoning in Children, editorial, Canad. M. A. J. **66**:278, 1952. Brown, R. J. K.: Ferrous Sulfate Poisoning in Children, correspondence, Brit. M. J. **1**:438, 1952. Acute Iron Poisoning, Nutrition Rev. **10**:299, 1952. Arnold, G. G.: Ferrous Sulphate Poisoning, South. Med. & Surg. **114**:36, 1952. Swift, S. C.; Cefalu, V., and Rubell, E. B.: Ferrous Sulfate Poisoning, J. Pediat. **40**:6, 1952.

345 (*a*) Peterson, R. E.: The Serum Iron in Acute Hepatitis, J. Lab. & Clin. Med. **39**:225, 1952. (*b*) Matassarin, B. J., and Delp, M. H.: The Relation of Serum Iron to Hepatocellular Damage, Am. J. M. Sc. **224**:622, 1952.

346. Butzengeiger, K. H., and Lange, J.: Über das Verhalten des Eisen- und Kupferspiegel im Blut bei Erkrankungen der Leber und Gallenwege, Deutsches, Arch. klin. Med. **199**:633, 1952.

347. Davidson, W. N., and Jennison, R. F.: The Relationship Between Iron Storage and Anemia, J. Clin. Path. **5**:281, 1952.

is no storage of iron in the marrow and the serum iron is low. In pernicious anemia the marrow and serum iron levels are elevated but fall after treatment. In the anemia of sepsis and uremia the marrow iron is high and the serum iron low. The highest levels of serum and marrow iron are found after multiple transfusions.

The iron tolerance test is advocated for differentiating endogenous hemochromatosis and cirrhosis, as previously mentioned.[348] Radioactive iron turnover studies have proved an extremely promising tool for evaluating erythroid production and for solving difficult problems[349]: for example, (1) to differentiate splenomegaly associated with extramedullary erythropoiesis from that associated with increased red cell destruction, (2) to differentiate refractive anemias with red cell hyperplasia from those with red cell hypoplasia, (3) to differentiate excessive iron turnover occurring through abnormal accessory nonerythrogenic pathways (as in certain carcinomas and in rheumatoid arthritis) from excessive turnover via red cells, (4) to determine erythrocyte production in polycythemia vera, and (5) to investigate many other problems of iron metabolism.[11]

Unusual iron metabolism has been noted in a patient with coexistent chronic lymphatic leukemia and polycythemia.[350] A kinetic model which provides a basis for rate computation for the movement of plasma iron has been hypothesized.[351] Administration of estrogen to rabbits of both sexes causes a rapid drop in serum iron levels in vivo but not in vitro; testosterone and progesterone have no effect.[352] Thorium dioxide injections produce hypoferremia and block the similar effects of turpentine.[353]

In dogs exposed to atomic irradiation a hormonal element is produced in the blood which decreases capillary sensitivity to epinephrine in rats. This vasodepressor material has been found to fit the criteria established for ferritin.[354] Chemical studies show that hemosiderin contains no ferritin and is not simply an accumulation of ferritin.[355]

Copper metabolism has been studied in the diet[356] and with reference to iron metabolism.[43f] Copper deficiency in swine produces an anemia indistinguishable

348. Gitlow, S. E.; Beyers, M. R., and Colmore, J. P.: Metabolism of Iron: II. Intravenous Iron Tolerance Tests in Laennec's Cirrhosis, J. Lab. & Clin. Med. **40**:541, 1952.

349. Footnote 10. Elmlinger and others.[11a]

350. Bethard, W. F.; Block, M., and Robson, M.: Morphologic and Metabolic Studies in a Case of Coexistent Chronic Lymphatic Leukemia and Polycythemia (Primary) with Particular Reference to Unusual Iron Metabolism, abstracted, J. Lab. & Clin. Med. **40**:779, 1952.

351. Huff, R. L.; Elmlinger, P.; Mortimer, R.; Anger, H., and Tobias, C. A.: A Model of Plasma Iron Kinetics in Human Subjects, abstracted, J. Clin. Invest. **31**:640, 1952.

352. Influence of Route of Administration and of Sex on Serum Iron Levels, Nutrition Rev. **10**:210, 1952.

353. Jensen, W. N.; Gubler, C. J.; Cartwright, G. E., and Wintrobe, M. M.: Anemia of Infection: XVIII. Effects of Turpentine and Colloidal Thorium Dioxide on Rat Plasma Iron Levels, Proc. Soc. Exper. Biol. & Med. **80**:33, 1952.

354. Haley, T. J.; Andem, M. R.; Riley, R. F., and Williams, I.: Identification of Ferritin in Blood of Dogs Subjected to Radiation from an Atomic Explosion, Proc. Soc. Exper. Biol. & Med. **79**:547, 1952. Corcoran, A. C.; Page, I. H.; Masson, G. M. C.; Taylor, R. D., and Dustan, H.: Hypertension and Hypertensive Cardiovascular Disease, A. M. A. Arch. Int. Med. **87**:732, 1951.

355. Behrens, M., and Taubert, M.: Über die Beziehungen zwischen Hämosiderin und Ferritin, Ztschr. physiol. Chem. **289**:116, 1952.

356. Kaufman, N.; Cartaya, J. A.; White, P. L.; Hegsted, D. M., and Kinney, T. D.: An Attempt to Produce Hemochromatosis Experimentally and the Effect of High Levels of Copper and Choline in the Diet, J. Nutrition **46**:433, 1952.

from iron deficiency anemia.[357] There is a negligible store of iron in the liver of newborn chicks.[358]

Methemoglobinemia: A review on the recognition, treatment, and prevention of methemoglobinemia[359] stresses the ease of absorption of nitro and amino compounds through the skin, digestive, and respiratory tracts and the need for early recognition of the disease. Methemoglobinemia, due to ingestion of acetophenetidin, may have caused the death of a newborn child, possibly by transplacental passage of the drug.[124b] Cyanosis in a month-old infant has been attributed to the presence of nitrates in well water used for preparing feedings.[360]

Treatment of methemoglobinemia requires removal of the offending agent, oxygen therapy, and administration of a reducing agent to break the oxide bond. Successful therapy in cases due to exposure to aniline, naphthalene, and after ingestion of children's wax crayons has been effected with oxygen and transfusions,[361] ascorbic acid,[362] and methylene blue,[363] respectively.

The hereditary form of methemoglobinemic cyanosis exists from birth and is inherited by both sexes. Congenital heart disease, arteriovenous shunt, polycythemia, and drug intoxication have been considered in the differential diagnosis.[364]

In one case of severe sulfhemoglobinemia the cause was not determined.[365] The chemistry of the methemoglobin-hydrogen peroxide complex has been studied.[366] Methemoglobin formation has also been used as a measure in the chemical analysis of aniline toxicity in cats.[367]

Porphyria: Porphyria is a disorder in the metabolism of pyrroles of unknown etiology and may be manifested by several clinical pictures. Uroporphyrin excretion is uniformly present, and its isolation and identification is the only reliable basis for diagnosis. Biochemically and clinically porphyria is further classified into three types: congenital, acute intermittent, and chronic, or tardive.[368] Photosensitiv-

357. Cartwright, G. E.; Gubler, C. J.; Lahey, M. E., and Chase, M. S.: The Relation of Copper to the Metabolism of Iron, J. Clin. Invest. **31**:620, 1952.

358. Ramsey, W. N. M.: Iron Metabolism and Hemoglobin Formation in the Embryonated Hen Egg, Biochem. J. **51**:289, 1952.

359. Mangelsdorff, A. F.: Methemoglobinemia-Recognition, Treatment, and Prevention, Indust. Med. **21**:395, 1952.

360. Campbell, W. A. B.: Methaemoglobinaemia Due to Nitrates in Well-Water, Brit. M. J. **2**:371, 1952.

361. Casciano, A. D.: Acute Methemoglobinemia Due to Aniline, J. M. Soc. New Jersey, **49**:141, 1952.

362. Richardson, J. D.: Methaemoglobinaemia, Brit. M. J. **2**:565, 1952. Johnston, N. A. F.: Methaemoglobinaemia, ibid. **2**:565, 1952.

363. Olson, R. A.: Methemoglobinemia Simulating Bulbar Poliomyelitis, California Med. **77**:151, 1952.

364. Codounis, A.: Hereditary Methaemoglobinaemic Cyanosis, Brit. M. J. **2**:368, 1952. Gasul and others.[124b]

365. Angove, R. C.: Sulphaemoglobinaemia of Unusual Severity, M. J. Australia **2**:815, 1952.

366. Dalziel, K., and O'Brien, J. R. P.: The Reaction of Methaemoglobin with Hydrogen Peroxide, Biochem. J. **52**:6, 1952.

367. Reiter, M., and Leusser, K.: Einfluss der Methylsubstitution auf die Hämoglobin-(Methämoglobin-) Bildung und die allgemeintoxizität des Anilins, arch. exper. Path. u. Pharmakol. **214**:158, 1952.

368. (*a*) Dillaha, C. J., and Hicklin, W.: Experimental Therapy of Chronic Porphyria with Vitamin B_{12}, J. Invest. Dermat. **19**:489, 1952. (*b*) Hill, R.: A Case of Idiopathic Porphyria, Brit. M. J. **2**:698, 1952.

ity occurs in the congenital and chronic types. Gastrointestinal, psychiatric, and neurologic symptoms are prominent in the acute intermittent type. The history of alcohol indulgence and functional impairment of the liver are frequent findings in the chronic cases.

A fascinating series of studies correlating clinical and experimental porphyria has been made by Schmid and co-workers.[369] They demonstrated that a hepatic as well as an erythropoietic porphyria can be produced experimentally in rabbits. In congenital or photosensitive porphyria the abnormal porphyrin formation originates in the normoblastic nuclei of the bone marrow (porphyria erythropoietica), while in the intermittent acute and the "mixed" types the origin is the liver (porphyria hepatica). A condition similar in many respects to the human erythropoietic porphyria, with high concentrations of uroporphyrin I in the marrow, circulating erythrocytes, and urine, has been achieved by treating rabbits with a combination of phenylhydrazine, intravenous lead acetate, and ultraviolet light. It has also been found that a condition with the essential features of human hepatic porphyria can be produced in rabbits by administration of allyl-isopropyl-acetyl-carbamide (Sedormid). These rabbits excrete urinary uroporphyrin and porphobilinogen even in excess of amounts found in the human disease. Thus the indication that the liver may produce porphyrins independent of hemoglobin synthesis in the marrow is of particular interest.

The hypothesis that genetic-controlled deficiencies may occur in the porphyrin enzyme system, with production of surplus pigment, has been proposed also. Subsequent temporary failure of the liver to excrete the surplus pigment would then produce the symptoms associated with porphyria.[370] No evidence has been found that either the excessive fecal proporphyrin or coproporphyrin is derived from destruction of circulating hemoglobin.[371] A temporary condition simulating porphyria occurred in seven patients with lead poisoning.[372]

Mistaken diagnosis of mild porphyria has been suggested to account for the unnecessary laparotomies done for acute abdominal emergencies.[373] In the diagnosis of several hundred cases of porphyria among European, Bantu, and colored patients in South Africa[374] the following points were stressed: recognition of skin lesions, intermittent porphyrinuria, necessity of repeated tests, characteristic retinal changes, and episodes of acute abdominal pain.

Therapy with vitamin B_{12}, in conjunction with alcoholic abstinence, was beneficial in one patient; no improvement occurred in two patients who continued

369. Schmid, R., and Schwartz, S.: Experimental Porphyria in Rabbits, abstracted, J. Clin. Invest. **31**:659, 1952. Schwartz, S.; Keprios, M., and Schmid, R.: Experimental Porphyria: II. Type Produced by Lead, Phenylhydrazine and Light, Proc. Soc. Exper. Biol. & Med. **79**:463, 1952. Schmid, R.; Hanson, B., and Schwartz, S.: Experimental Porphyria: I. Isolation of Uroporphyrin I from Bone Marrow of Lead Poisoned Rabbits, ibid. **79**:459, 1952.

370. Rimington, C.: Haems and Porphyrins in Health and Disease, Acta med. scandinav. **143**:161, 1952.

371. Lowry, P. T.; Hawkinson, V., and Watson, C. J.: An Isotopic Study of Type III Porphyrins and Hemoglobin Metabolism in an Unusual Case of "Mixed" Porphyria, Metabolism **1**:149, 1952.

372. Kench, J. E.; Lane, R. E., and Varley, H.: Urinary Coproporphyrins in Lead Poisoning, Brit. J. Indust. Med. **9**:133, 1952.

373. Williams, C. J., and Lothian, K. R.: Two Cases of Acute Idiopathic Porphyria, Brit. M. J. **2**:375, 1952.

374. Marshall, J.: Porphyria, Brit. M. J. **2**:833, 1952.

alcohol intake.[368a] Splenectomy reduces excretion of porphyrin in the urine and of urobilinogen in the feces, but does not affect hematologic findings and skin sensitivity to light.[375] One patient with acute porphyria treated with corticotropin experienced clinical improvement,[376] but there was no change in uroporphyrin excretion. Dimercaprol (BAL; British Anti-Lewisite; 2,3-dimercaptopropanol) produced distinct improvement in one patient, with regression of skin lesions and urinary changes.[377]

Hemolytic Syndromes.—Hemolytic anemias may be the result of either (1) intracorpuscular defects or (2) extrinsic factors acting on the erythrocyte. Shape anomalies are generally the primary evidences of intrinsic defects.[378] Anemia results only when the hemolytic process overtaxes the regenerative capacity. Compensatory marrow hyperplasia is able to maintain the equilibrium until the average erythrocyte survival is diminished to 15 to 20 days.[379]

Clinical and Laboratory Experimental Studies Associated with Red Blood Cell Destruction: Physical studies. Stromata prepared by numerous lytic methods appear to be characteristically different. Therefore, Ponder has emphasized the necessity for stipulating the method used.[380] Electronic microphotographs provide an interesting approach to the study of the erythrocyte membrane.[381] Erythrophagocytosis has been found increased in acquired hemolytic anemia[382] and in paroxysmal cold hemoglobinuria.[383] In vitro techniques to determine the susceptibility of test erythrocytes to phagocytosis have been described and applied to the cells of acquired hemolytic anemia[382] and to trypsinized, sensitized, irradiated, and spherocytic erythrocytes.[384] Reticulocytes have been shown to be more resistant to hypotonic saline than normal cells.[385]

Sludged blood is hypothesized to have numerous ramifications[386]: (1) hypoxia, causing increased capillary permeability; (2) phagocytosis of the sludged cells (we have shown that erythrocytes taken from persons having marked intravascular

375. Gray, C. H., and Neuberger, A.: Effect of Splenectomy in a Case of Congenital Porphyria, Lancet **1**:851, 1952.

376. Goldberg, A.; MacDonald, A. C., and Rimington, C.: Acute Porphyria, Experimental Treatment with A.C.T.H., Brit. M. J. **2**:1174, 1952.

377. Schrumpf, A.: Porphyria Treated with Dimercaprol, Lancet **2**:1226, 1952.

378. Zuelzer, W. W.: Hemolytic Anemias: Mechanisms and Diagnostic Aspects, J. Pediat. **41**:479, 1952.

379. Crosby, W. H., and Akeroyd, J. H.: The Limit of Hemoglobin Synthesis in Hereditary Hemolytic Anemia, Am. J. Med. **13**:273, 1952.

380. Ponder, E.: Various Types of Ghosts Derived from Human Red Cells: Heat Fragmentation and Phase Optics Studies, J. Exper. Biol. **29**:605, 1952. A Mechanical Fragmentation Phenomenon Observed in Fixed Red Cells and Ghosts, Acta haemat. **8**:155, 1952.

381. Hug, O.; Lippert, W., and Moser, P.: Morphologische Veränderungen der Erythrocyten bei der Hypotonischhämolyse, Arch. exper. Path. u. Pharmakol. **214**:308, 1952. Latta.[142]

382. Zinkham, W. H., and Diamond, L. K.: In Vitro Erythrophagocytosis in Acquired Hemolytic Anemia, Blood **7**:592, 1952.

383. Jordan, W. S.; Prouty, R. L.; Heinle, R. W., and Dingle, J. H.: The Mechanism of Hemolysis in Paroxysmal Cold Hemoglobinuria: III. Erythrophagocytosis and Leukopenia, Blood **7**:387, 1952.

384. Wright, C. S.; Dodd, M. C.; Bass, J. A., and Brandt, N. G.: The Normal and Modified Erythrocyte: Observations of Certain Phagocytable Characteristics, abstracted, J. Clin. Invest. **31**:674, 1952.

385. Cruz, W. O., and Junqueira, P. C.: Resistance of Reticulocytes and Young Erythrocytes to the Action of Specific Hemolytic Serum, Blood **7**:602, 1952.

386. Boines, G. J.: Sludged Blood in Poliomyelitis, Delaware M. J. **24**:43, 1952.

sludging do not show an increased susceptibility to phagocytosis as tested with a recently described in vitro technique[387]; (3) thrombus formation with possible resulting emboli, and (4) intermittent vasoconstriction in selected tissues. Electron micrographs show surface coatings on sludged erythrocytes.[388] In active tuberculosis there is correlation between sludging, the sedimentation rate, and the extent of the lesion.[389]

The anemia of lead poisoning in guinea pigs has been studied with a reticuloendothelial blockade and splenectomy. Lead poisoning modifies the erythrocyte precursors and hastens their removal from circulation by the spleen and reticuloendothelial system. Therefore, both hemopoiesis and hemolysis appear to play a role in the anemia of chronic lead poisoning.[390]

Chemical studies. Among a large number of unrelated chemical substances influencing hemolysis are a lysolipid, prepared by the action of snake venom on egg yolk[391]; α-tocopherol and hydrogen peroxide[392]; cation soaps[393]; silver ions[394]; and tissue lysins extracted from fresh liver, kidney, and testes of rabbit, guinea pig, rat, and cattle.[395] The development of cation permeability is disclaimed as a direct cause of hemolysis in glucose solutions.[396]

Immune phases of hemolysis. Several years ago anti-human-globulin serum (Coombs) was suggested as a means of demonstrating incomplete antibodies on the cells of patients with idiopathic acquired hemolytic anemia, thus differentiating it from hereditary spherocytosis. This differentiation is not as clear cut as was initially suggested, because incomplete antibodies have been demonstrated by the Coombs and/or trypsinized red cell test in practically the entire spectrum of hemolytic disease.[397] Further work on the anti-human-globulin serum (Coombs) separated it into two fractions; Fraction I was obtained by absorption with cells sensitized by Dacie's cold incomplete antibody and Fraction II by absorption with

387. Wright, C. S.; Dodd, M. C.; Brandt, N. G.; Elliott, S. M., and Bass, J. A.: Erythrophagocytosis: Standardization of a Quantitative Tissue Culture Test and Its Application to Hemolytic, Malignant, and Infectious Disease, J. Lab. & Clin. Med. **41**:169, 1953.

388. Bloch, E. H., and Powell, A.: Electron Microscopy of Human Erythrocytes from Healthy and Sludged Blood, Science **115**:46, 1952.

389. Knisely, M. H.; Gregg, D. B.; Jeffords, V.; Knisely, W., and Othersen, B.: Correlation of Intravascular Sludge in Vitro Sedimentation Rates and the Clinical Condition in Active Human Pulmonary Tuberculosis, Anat. Rec. **112**:351, 1952.

390. Pirrie, R.: The Effect of Splenectomy and Reticulo-Endothelial Blockade upon the Anaemia of Lead Poisoning in Guinea-Pigs, J. Path. & Bact. **64**:211, 1952.

391. Collier, H. B.: Factors Affecting the Hemolytic Action of "Lysolecithin" upon Rabbit Erythrocytes, J. Gen. Physiol. **35**:617, 1952.

392. Gordon, H. H., and de Metry, J. P.: Hemolysis in Hydrogen Peroxide of Erythrocytes of Premature Infants: Effect of Alphatocopherol, Proc. Soc. Exper. Biol. & Med. **79**:446, 1952.

393. Breusch, F. L., and Hersek, S.: Hämolyse durch Kationseifen, Ztschr. physiol. Chem. **291**:1, 1952.

394. Remmer, H., and Seiler, E.: Der Einfluss einer Hitzebehandlung roter Blutkörperchen auf die Silberwirkung, Arch. exper. Path. u. Pharmakol. **214**:272, 1952.

395. McElroy, O.; Jordan, W., and Freeman, M. E.: Tissue Hemolysins, Science **115**: 39, 1952.

396. Hendry, E. B.: Delayed Hemolysis of Human Erythrocytes in Solutions of Glucose, J. Gen. Physiol. **35**:605, 1952.

397. Wright, C. S.; Dodd, M. C.; Bouroncle, B. A.; Doan, C. A., and Zollinger, R. M.: Studies of Hemagglutinins in Hereditary Spherocytosis and in Acquired Hemolytic Anemia: Their Relationship to the Hypersplenic Mechanism, J. Lab. & Clin. Med. **37**:165, 1951.

Rh-sensitized cells.[398] In an attempt to produce a hemolytic syndrome in rabbits Liu and Evans found that in 3 of 12 animals a positive antiglobulin test developed after the received intraperitoneal injections of homologous blood.[399]

The reversibility of the red cell antibody reaction has been demonstrated by experiments which transfer the antibody either from red cell stromata to intact erythrocytes or from erythrocyte to erythrocyte.[400] Intact azoerythrocytes sensitized with antisera homologous to the attached azo-grouping are hemolyzed by addition of complement.[401]

Further study of fava bean sensitization again suggests an immunologic dysfunction.[402]

Hemagglutinins are present in a wide variety of animals and plants. The hemolymph of the larva and pupa of the Cecropia moth exhibits a strong labile agglutinin for washed mammalian cells, while that of closely related butterfly larvae is negative.[403]

Virus and enzyme studies in the hemolytic syndromes. Considerable interest and speculation has been aroused by the isolation of the Newcastle disease virus from patients with hemolytic anemias by Moolten and his associates.[404]

It has long been known that viruses are adsorbed by erythrocytes and can significantly change the surface characteristics. In fact, erythrocyte adsorption and elution are used in the measurement of viruses. Virus modification may render the erythrocyte more susceptible to phagocytosis [405] and/or lower the surface charge.[406] Thus the virus-modified erythrocyte becomes of interest in red cell destruction. The virus-erythrocyte interaction has been studied by Melnick with the electron

398. Renton, P. H.: Separation of Coombs Reagent into 2 Fractions, Nature, London, **169**:329, 1952.

399. Liu, C. K., and Evans, R. S.: Production of Positive Antiglobulin Serum Test in Rabbits by Intraperitoneal Injection of Homologous Blood, Proc. Soc. Exper. Biol. & Med. **79**:194, 1952.

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402. Creger, W. P., and Gifford, H.: Some Interrelationships of Blood and the Fava Bean Principle in Vitro, Blood **7**:721, 1952.

403. Bernheimer, A. W.: Hemagglutinins in Caterpillar Bloods, Science **115**:150, 1952.

404. (*a*) Moolten, S. E., and Clark, E.: Viremia in Acute Hemolytic Anemia and in Autohemagglutination: Report of a Case and Review of the Literature with Special Reference to the Virus of Newcastle Disease, A. M. A. Arch. Int. Med. **89**:270, 1952. (*b*) Dameshek, W.: Viruses and Some Blood Dyscrasias, Editorial, Blood **7**:560, 1952. (*c*) Briody, B. A.: Action of Viruses on Red Blood Cells, Tr. New York Acad. Sc. **14**:231, 1952. (*d*) Moolten, S. E., and Clark, E.: The Red Blood Cell as a Vehicle of Virus Transport: I. Isolation and Identification of Blood-Borne Viruses; II. Role of Blood-Borne Viruses in Autohemagglutination and in Hemolytic Anemia, ibid. **14**:232, 1952. (*e*) Stats, D., and Wasserman, L. R.: A Critique of Our Knowledge of the Etiology of Hemolytic Anemia, ibid. **14**:238, 1952. (*f*) Morgan, H. R.: Acquired Hemolytic Anemia and Viremia, J. Lab. & Clin. Med. **40**:924, 1952.

405. Wright, C. S.; Dodd, M. C.; Bass, J. A., and Wallace, J.: Additional Studies in Erythrophagocytosis, to be published.

406. Ada, G. L., and Stone, J. D.: Electrophoretic Studies of Virus-Red Cell Interaction, Brit. J. Exper. Path. **31**:263, 1950.

microscope and summarized as follows:[407] (1) viruses are first seen on the cell surface, (2) then the virus particles enter the body of the cell, and (3) this is followed by elution of the adsorbed particles, leaving the cell surface roughened. Electron microscope evidence also demonstrates that the erythrocyte membranes do not accept the influenza virus a second time after a fixation-separation process.[408]

The use of trypsin-modified erythrocytes for demonstrating incomplete antibodies in hemolytic anemias has stimulated attention to the entire field of enzyme-treated red cells. Recent studies were made on the following phases: the reaction of incomplete Rh antibodies with papain-sensitized cells,[409] the agglutination mechanism of trypsin-modified red cells,[410] the effect of human serum upon the agglutination of enzyme-modified cells,[411] and the increased susceptibility of trypsinized erythrocytes to phagocytosis.[412]

The life span of the transfused erythrocyte in vivo. The life span may be measured by (1) tagging erythrocytes with radioactive isotopes of phosphorus (P^{32}), chromium (Cr^{51}), iron (Fe^{55}, Fe^{59}), and carbon (C^{14}); (2) chemically labeling and hemoglobin, i. e., using sulfhemoglobin; (3) using a morphologically recognizable erythrocyte, i. e., the sickle cell; (4) using differential agglutination techniques (Ashby) as the basis to distinguish donor from recipient cells.[413] These techniques have been extremely valuable as investigative tools and occasionally as direct clinical laboratory techniques.

Clinical Hemolytic Anemias: Idiopathic acquired hemolytic anemia. Idiopathic acquired hemolytic anemia and the associated immunologic phenomena have been reviewed by Sacks and co-workers.[414] The disease in children has been surveyed by Millichap.[415] Whether the antibodies demonstrated by the antiglobulin (Coombs), the albumin, and the trypsinized red cell tests are the cause or the result is still a matter of conjecture. There is no correlation between the antibody titer and the severity of the hemolysis.

Hemolytic anemias secondary to other diseases. A number of instances of acquired hemolytic anemia develop as complications of generalized systemic diseases. Among

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407. Melnick, J. L.: Second National Cancer Conference, Cincinnati, Ohio, March 3-5, 1952.

408. Bolt, W.; Kuchenhoff, O., and Vogel, T.: Elektronenoptische Studien über Grippevirus und das Bindungs-Lösungsphänomen an der Erythrocytenmembran, Deutsche med. Wchnschr. **76**:17, 1951.

409. Zwicker, H.; Giordano, L., and Hoyt, R. E.: Studies on Reactions of Incomplete Rh Antibodies With Enzyme Treated Rh Positive Red Cells, J. Immunol. **69**:415, 1952.

410. Dausset, J.: The Agglutination Mechanism of Trypsin Modified Red Cells, Blood **7**:816, 1952.

411. Hoyt, R. E., and Zwicker, H.: The Effect of Human Serum Upon the Agglutination of Enzyme-Treated Erythrocytes, J. Immunol. **68**:61, 1952.

412. Wright, C. S.; Dodd, M. C.; Bouroncle, B. A.; Elliott, S. M.; Baxter, J. A., and Bass, J. A.: A Study of the Physical, Phagocytable, and Immunologic Aspects of the Trypsinized Erythrocyte, abstracted, J. Lab. & Clin. Med. **38**:962, 1951. Brandt, N. G.; Bass, J. A.; Dodd, M. C., and Wright, C. S.: Phagocytosis of Normal, Sensitized and Trypsinized Erythrocytes by Tissue Culture Macrophages, abstracted, Fed. Proc. **11**:462, 1952.

413. Berlin, R., and Hedenstedt, S.: The Life Span of Elliptocytes, Acta med. scandinav. **143**:273, 1952.

414. Sacks, M. S.; Workman, J. B., and Jahn, E. F.: Diagnosis and Treatment of Acquired Hemolytic Anemia, J. A. M. A. **150**:1556, 1952.

415. Millichap, J. G.: Acute Idiopathic Haemolytic Anaemia, Arch. Dis. Childhood **27**:222, 1952.

these are kala-azar [416]; lupus erythematosus disseminatus [417]; periarteritis nodosa [418]; myeloid metaplasia of the spleen [419]; ovalocytosis [420]; lymphosarcoma and reticulum cell sarcoma [421]; chronic leukemias, particularly the lymphocytic type,[422] and generalized reticulosis.[423] Therapy is discussed on page 410.

Hereditary spherocytosis. The state of the marrow during hemolytic crisis in hereditary spherocytosis continues to attract interest. Battle [424] reports three instances of hypoplastic marrow in crisis which were assertedly caused by infection, thus supporting Owren's "central marrow depression" theory of hemolytic crisis. Undoubtedly, the hypoplastic phase in certain rare crises does occur; however, it does not exist in all crises of hereditary spherocytosis. Erythroid hyperplasia in the marrow is the rule. In observing hemolytic crises of five members of a family, Ingram [425] claimed infection played no part. Another potential influence of infection in precipitating a hemolytic crisis may be a peripheral one, in contradistinction to Owren's "central" hypothesis. Viral infections may assist in the trigger mechanism of the peripheral crisis in hereditary spherocytosis as it does in acquired hemolytic anemias.[404a] The relation of viruses and red cell destruction is discussed on page 399.

Gall bladder symptoms may be the presenting difficulty in hereditary spherocytosis. Of 152 patients investigated, 43% had biliary disease. The incidence of this complication in hereditary spherocytosis is decreased by early splenectomy, which corrects the increased hemolysis.[426]

416. Rachmileqitz, M.; DeVries, A., and Gurevitch, J.: Further Observations on the Anemia in Kala-Azar, Acta haemat. **7**:179, 1952.

417. Dubois, E. L.: Acquired Hemolytic Anemia as the Presenting Syndrome of Lupus Erythematosus Disseminatus, Am. J. Med. **7**:197, 1952.

418. Lovshin, L. L.: Association of Acquired Hemolytic Anemia with Periarteritis Nodosa, Cleveland Clin. Quart. **19**:28, 1952.

419. Claman, M. A., and Collier, W.: Acute Hemolytic Anemia Associated with Myeloid Metaplasia of the Spleen, A. M. A. Arch. Int. Med. **89**:431, 1952.

420. Wilson, H. E., and Long, M. J.: Ovalocytosis with Hypersplenism: Report of 2 Cases and Observations on the Pathogenesis of the Hypersplenism, Proceedings, American Federation Clinical Research, National Meeting, Atlantic City, N. J., May 4, 1952.

421. Wilcox, D. R. C.: Haemolytic Anaemia and Reticulosis, Brit. M. J. **1**:1322, 1952.

422. (*a*) Sokoloff, B.; Eddy, W. H.; Beaumont, J.; Powella, R., and Cone, G.: The Effect of an Ascorbic Acid Analog on Ascorbic Acid Content and White Blood Cells of Ak Leukemic Mice, Cancer Res. **12**:298, 1952. (*b*) Schilling, R. F.: The Mechanical Fragility of Erythrocytes from Leukemic Patients, J. Lab. & Clin. Med. **40**:939, 1952. (*c*) Fisher, J. H.; Welch, C. S., and Dameshek, W.: Splenectomy in Leukemia and Leukosarcoma, New England J. Med. **246**:483, 1952. (*d*) Henie, F., and Blessing, K.: Panagglutination, Eigenagglutination der gewaschenen Patienten-Blutkörperchen und Agglutinationshemmung durch Plasmaalbumin bei erworbener hämolytischer Anämie, Acta haemat. **8**:232, 1952. (*e*) Ross, J.; Crockett, C. L., Jr.; Finch, S. C., and Emerson, C. P.: The Mechanism of Anemia in Leukemia and Malignant Lymphoma, Read Before Second National Cancer Conference, Cincinnati, March 3-5, 1952. (*f*) Cartwright, G. E.: Mechanism of Anemia in Lymphomas and Leukemia, Read Before Second National Cancer Conference, Cincinnati, March 3-5, 1952.

423. Farquhar, J. W., and Claireaux, A. E.: Familial Haemophagocytic Reticulosis, Arch. Dis. Childhood **27**:519, 1952.

424. Battle, J. D.: Hereditary Spherocytosis (Congenital Hemolytic Jaundice): Pathogenesis of the "Hemolytic" Crisis, Am. J. M. Sc. **224**:82, 1952.

425. Ingham, W. N.: A Familial Crisis in Congenital Acholuric Jaundice, Arch. Dis. Childhood **27**:34, 1952.

426. Bates, G. C.; Brown, C. H., and Bunts, F. E.: Incidence of Gallbladder Disease in Chronic Hemolytic Anemia (Spherocytosis), Gastroenterology **21**:104, 1952.

Hemoglobinuria. 1. Paroxysmal nocturnal hemoglobinuria. Paroxysmal nocturnal hemoglobinuria is characterized by intravascular hemolysis and hemoglobinuria generally induced during sleep. The hemolysis results from the action of at least two serum factors, one heat labile and magnesium dependent and the other an absorbable globulin.[427] The heat-labile factor must react with the cells prior to the absorbable factor for hemolysis to occur.

In cases of paroxysmal nocturnal hemoglobinuria with pancytopenia and mild hemoglobinuria the diagnosis may be confused with aplastic or "refractory" anemias.[428]

2. Paroxysmal cold hemoglobinuria. Paroxysmal cold hemoglobinuria may be due to one of two fundamental mechanisms, i. e. (1) the paroxysmal cold hemoglobinuria associated with a positive Donath-Landsteiner reaction and positive syphilitic serology and (2) paroxysmal cold hemoglobinuria characterized by a high titer of cold agglutinins in the serum of the patient. Van Loghem and his associates[429] list the following differentiations:

"Classic" P. C. H.	P. C. H. Caused by Cold Agglutinins
1. No cold agglutinins in high titer	1. Cold agglutinins in high titer present
2. Donath-Landsteiner reaction positive	2. Donath-Landsteiner reaction negative or nonspecific
3. Wassermann reaction positive	3. Wassermann reaction negative or incidentally positive
4. Complement necessary for hemolysis	4. Complement not necessary for hemolysis
5. Dermolysin present	5. Dermolysin absent
6. Rashes of cold urticaria frequently observed during attack	6. No rashes of cold urticaria
7. Vascular disorders absent	7. Vascular disorders (Raynaud syndrome) frequently present
8. Antiluetic treatment successful	8. Antiluetic and other treatment unsuccessful. (In recent publications favorable effect is noticed after combined treatment with vitamin D, estradiol and thyroid.)

Fifteen cases of paroxysmal cold hemoglobinuria of the syphilitic type were collected from 951,855 hospital and clinic admissions.[430] Simultaneously occurring cold and acid hemolysins were present in a patient with paroxysmal cold hemoglobinuria.[121] In the Donath-Landsteiner-positive group there may be many variations of the thermostability, optimal period of the cold phase, and the need of complement for the fixation of the antibody in the cold. Complement has been found to be reduced or absent in both types.[429] Cold agglutinins are paramount in

427. Clapp, M. P.; Williams, M. J., and Mendel, J. L.: Observations on the Hemolytic Mechanism of Paroxysmal Nocturnal Hemoglobinuria: Demonstration of the Activity of at Least 2 Serum Factors in P N H Hemolysis, Blood **7**:1117, 1952.

428. Letman, H.: Possible Paroxysmal Nocturnal Hemoglobinuria With Pronounced Pancytopenia, Reticulocytopenia, and Without Hemoglobinuria Simulating Aplastic Anemia, Blood **7**:842, 1952.

429. van Loghem, J. J.; Mendes de Leon, D. E.; Frenkel-Tietz, H., and van der Hart, M.: Two Different Serologic Mechanisms of Paroxysmal Cold Hemoglobinuria, Illustrated by Three Cases, Blood **7**:1196, 1952.

430. Hall, B. D.: Paroxysmal Cold Hemoglobinuria, U. S. Armed Forces M. J. **3**:1519, 1952.

the second type; however, occasionally hemolysins also assist in the red cell destruction. Warning has been given that transfusions with fresh whole blood may, by adding complement, precipitate hemolysis of the patient's own cells as well as of the transfused cells.

Therapy in the cold agglutinin type has been particularly discouraging and has been centered primarily around protection from the cold.[431]

Study of renal function has demonstrated that the free circulating hemoglobin causes specific renal hemodynamic changes whether the source be endogenous or exogenous.[432] Renal damage as the cause of death in paroxysmal cold hemoglobinuria is not infrequent.

The erythrophagocytosis and leucopenia associated with the Donath-Landsteiner-positive paroxysmal cold hemoglobinuria have been studied in vivo and in vitro.[383] Maximum phagocytic activity is observed at the time of cold-induced crises.

Sickle cell anemia and thalassemia. Sickle cell anemia (drepanocytic anemia, meniscocytosis, Herrick's disease) and thalassemia (Mediterranean, hereditary leptocytosis, Cooley's anemia) have received much attention.[433]

1. Incidence. In Africa the incidence of sickle cell anemia is low [434] and that of the trait high,[435] in contrast to the opposite ratio in the United States. The hypothesis that the sickling gene causes anemia only when inherited with another gene or genes derived from an European ancestor has been suggested to account for the trait-anemia differences in African populations.[436] In the Belgian Congo, all mothers of patients with sickle cell anemia showed the trait.[437] A high percentage of persons possessing the trait has been found also in the district of Accra along the Gold Coast,[438] in Nigera,[434b] and in Greece.[439] The fourth case of sickle cell anemia in a white adult in Greece was reported by Zaberdinos.[440] The trait is rare among Arabs and is practically nonexistent among Yemenite Jews.[441] There is an increased incidence of the disease in Negroes with tuberculous infection.[442]

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431. Sweetman, W. P.; Murphy, E. F., and Woodcock, R. C.: Acute Idiopathic Paroxysmal Cold Hemoglobinuria of Non-Syphilitic Type in a Child, Brit. M. J. **1**:463, 1952.

432. Brandt, J. L., and Lichtman, H. C.: Paroxysmal Cold Hemoglobinuria: Renal Function Studies During an Induced Hemolytic Episode, Proceedings, American Federation Clinical Research, National Meeting, Atlantic City, N. J., May 4, 1952.

433. Caminopetros, J.: The Sickle-Cell Anomaly As a Sign of Mediterranean Anemia, Lancet **1**:687, 1952. Ashman, R.: Are Certain Blood Dyscrasias an Effect of Racial Mixture? Am. J. Phys. Anthropol. **10**:217, 1952. Schubothe, H.: Die korpuskulären hämolytischen Erkrankungen, Deutsche med. Wchnschr. **77**:1515, 1952. Rogers, G. W.: Sickle Cell Anemia, an Hematologic Challenge, Mississippi Doctor **29**:193, 1952. Margolies, M. P.: Sickle Cell Anemia, Medicine **30**:357, 1951.

434. (*a*) Griffiths, S. B.: Sickle Cell Trait in Africans, Brit. M. J. **2**:441, 1952. (*b*) Jelliffe, D. B., and Humphreys, J.: Sickle Cell Trait in Western Nigeria, ibid. **1**:405, 1952.

435. Sickle Cell Anemia in Africa, Editorial, Brit. M. J. **2**:433, 1952.

436. The Sickle-Cell Trait, Editorial, Brit. M. J. **1**:426, 1952.

437. Vandepitte, J. M.: Sickle Cell Anemia in Africa, Brit. M. J. **1**:920, 1952.

438. Edington, G. M.: Sickle-Cell Trait in the Newborn, Correspondence, Brit. M. J. **1**:763, 1952.

439. Caminopetros, J.: Sickle-Cell Anomaly in Greece, Correspondence, Lancet **1**:1212, 1952.

440. Zaberdinos, A.: Sickle Cell Anemia in a White Adult, J. A. M. A. **148**:549, 1952.

441. Dreyfuss, F., and Benyesch, M.: Sickle Cell Trait in an Arab, Lancet **1**:1213, 1952. Dreyfuss and others.[170]

442. Weiss, W.; Waife, S. O., and Stecher, W.: The Influence of the Sickling Phenomenon on the Incidence and Type of Tuberculosis, Proceedings, American Federation Clinical Research, National Meeting, Atlantic City, N. J., May 4, 1952.

The hypothesis that the population of most of tropical Africa contains a component derived from Asia has been proposed.[436] The trait appears in 30% of the Urulas, an aboriginal tribe of Southern India. This is a higher frequency than in most African populations.[443] From the Rh discrepancy of the Africans and Indians it is probable that the sickle cell trait was inherited from a common non-African ancestor to the northeast of Africa.[435] Sickle cell anemia has been found to occur in a small number of persons in Upper Assam (India).[444]

An explanation of how the sickling gene has been maintained in view of the fact that the homozygous persons die before puberty is that it is believed due to a positive selection of the heterozygote.[445] Another explanation claims that the trait and the anemia have independent genes.[435] This is discussed further in the following section. The low incidence of sickle cell anemia in newborn babies is attributed to the persistence of fetal hemoglobin in the first weeks of extrauterine life.[434b] Three cases of heterozygous thalassemia have been reported in Australia, and in all the patients were of Mediterranean origin.[446]

2. Genetics. (*a*) Sickle cell anemia. Neel observed that the blood of both parents of a patient with sickle cell anemia could be induced to sickle. It has been postulated [447] and confirmed [448] that a gene in the heterozygous state produces the trait and in the homozygous state produces anemia. There is no evidence for a linkage between the sickling gene and those genes responsible for the M, N, and S antigens.[449] Electrophoretic study of the hemoglobin solution from the mother of a patient with sickle cell anemia demonstrated the presence of a small amount (5%) of sickling ("S") type hemoglobin. Her cells did not sickle. This supports the concept that SCA develops only when both parents transmit the gene for "S" hemoglobin.[450]

(*b*) Thalassemia. Thalassemia is proposedly transmitted by an incompletely dominant autosomal gene which in the homozygous state causes thalassemia major and in the heterozygous state causes thalassemia minor. No evidence of linkage between thalassemia and genes for blood antigens has been found.[451] The genes

443. Lehmann, H., and Cutbush, M.: Sickle Cell Trait in Southern India, Brit. M. J. **1**:404, 1952.

444. Dunlop, K. J., and Mozumder, U. K.: The Occurrence of Sickle Cell Anaemia Among a Group of Tea Garden Labourers in Upper Assam, Indian M. Gaz. **87**:387, 1952.

445. Brain, P.: Sickle-Cell Anaemia in Africa, Brit. M. J. **2**:880, 1952.

446. Terrutt, A. H.: Mediterranean Anaemia, Report of 3 Cases, M. J. Australia **1**:885, 1952.

447. Neel, J. V.: Perspectives in the Genetics of Sickle Cell Disease, Blood **7**:467, 1952.

448. (*a*) Neel, J. V.; Schull, W. J., and Shapiro, H. S.: Absence of Linkage Between the Genes Responsible for the Sickling Phenomenon, the M N Blood Types, and the S-Agglutinogen, Am. J. Human Genetics **4**:204, 1952. (*b*) Schwartz, S. O.; Fitzpatrick, W. J., and Mason, J.: Incidences of Sickle Cell Disease, Acta haemat. **7**:43, 1952. (*c*) Vandepitte.[437]

449. Waller, M.; Waller, R. K., and Hughes, R. D.: Linkage Studies of Genes for Sickling and MNS Blood Groups: Negative Findings, Proc. Soc. Exper. Biol. & Med. **80**:479, 1952. Neel, Schull, and Shapiro.[448a]

450. Singer, K., and Fisher, B.: Studies on Abnormal Hemoglobins: 6. Electrophoretic Demonstration of Type S (Sickle Cell) Hemoglobin in Erythrocytes Incapable of Showing the Sickle Cell Phenomenon, Proceedings, American Federation Clinical Research, Midwest Section, Chicago, Nov. 6, 1952.

451. Ludwin, I.; Limentani, D., and Dameshek, W.: Linkage Tests of Mediterranean Anemia with Blood Groups, Blood Types, Rh Factors and Eye Color, Am. J. Human Genetics **4**:182, 1952.

of sickle cell anemia and thalassemia trait are located on different chromosomes and are inherited independently.[452]

Attempts have been made to correlate the genetic aspects of thalassemia with tissue culture differentiation and proliferation of erythroblasts.[453]

(*c*) Microdrepanocytic disease. A total of four cases of this condition (all of apparent Mediterranean origin) have been reported.[454] In each instance it was concluded that one parent had the gene for the sickle cell trait and the other parent the gene for thalassemia.

While this review was in press, Neel, Kaplan, and Zuelzer clarified considerably the genetic and clinical pictures of certain of these inherited erythrocyte disorders (sickling phenomenon and thalassemia).[454a] Although some of their conclusions are hypothetical, there seem to be several distinct hematologic dyscrasias associated with the sickling gene, among which are sickle cell disease (homozygosity for the gene responsible for the sickling phenomenon) sickle cell-hemoglobin-C disease (presence of both the sickle cell gene and the hemoglobin-C gene), and sickle cell-thalassemia disease (simultaneous presence of the sickle cell gene and the thalassemia gene). (Hemoglobin-C is a recently recognized abnormality of hemoglobin, which is readily demonstrated by electrophoretic methods and which may be suspected in the presence of abnormally large numbers of target cells.) Neel and his associates have shown that these blood dyscrasias can be differentiated by relatively simple methods. Reference to the original article is suggested.[454a]

3. Physical and chemical aspects of sickle cell anemia. In an excellent review Itano has discussed the physical-chemical bases for the earlier studies on normal and abnormal human hemoglobin and has stressed the need for avoidance of inhomogenous preparations in current studies.[21a] Five types of hemoglobin have been described: normal fetal, normal adult, sickle cell, and two other abnormal hemoglobins.[21a] One of the latter two, an alkali-resistant compound closely related to the physiologically occurring fetal pigment, has been designated as Type F, and the sickle cell hemoglobin, type S.[20b] Based on the uneven distribution of the F pigment within the erythrocyte population of patients with sickle cell anemia, a division of the red cells of such patients has been proposed: (1) cells containing S hemoglobin and no or little F; these have the shortened life span; (2) cells containing both pigments, and (3) cells containing F pigment with no or little S hemoglobin; these have the longest survival time and are most resistant to mechanical trauma.[20b]

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452. Silvestroni, E., and Bianco, I.: Genetic Aspects of Sickle Cell Anemia and Microdrepanocytic Disease, Blood **7**:429, 1952.

453. Astaldi, G., and Tolentino, P.: Studies on the Pathogenesis of Thalassaemia, J. Clin. Path. **5**:140, 1952.

454. Wasserman, C. F.; Phelps, V. R., and Hertzog, A. J.: Chronic Hemolytic Anemia in a White Child Due to Thalassemia and Sicklemia with a Genealogic Survey, Pediatrics **9**:286, 1952. Sturgeon, P.; Itano, H. A., and Valentine, W. N.: Chronic Hemolytic Anemia Associated with Thalassemia and Sickling Traits, Blood **7**:350, 1952. Battle and Lewis.[21b]

454a. Neel, J. V.; Kaplan, E., and Zuelzer, W. W.: Further Studies on Hemoglobin C: I. A Description of Three Additional Families Segregating for Hemoglobin C and Sickle Cell Hemoglobin, Blood **8**:724, 1953. Kaplan, E.; Zuelzer, W. W., and Neel, J. V.: Further Studies on Hemoglobin C: II. The Hematologic Effects of Hemoglobin C Alone and in Combination with Sickle Cell Hemoglobin, ibid. **8**:735, 1953.

The alkali-resistant component has been found to be identical electrophoretically and spectrophotometrically with normal fetal hemoglobin.[455] Tactoid and gel formation can be elicited with the reduced S compound but not with the alkali-resistant F hemoglobin fraction.[456]

Immune rabbit serum to sickle cell anemia erythrocytes is useful as a diagnostic aid.[22]

The turnover time of phosphorus in the sickle cell anemia erythrocytes, measured with radioactive phosphorus (P^{32}) in vitro, is approximately two and one-half times greater than that in the normal erythrocyte. The phosphorus turnover time of the sickle cell trait is intermediate.[457] Deoxygenated, but not the oxygenated, sickle cell anemia erythrocytes lose potassium and gain sodium almost immediately; during the first half hour the potassium-sodium exchange can be reversed by reoxygenation.[458]

4. Complications. (*a*) Sickle cell anemia. Conception occurs fairly frequently in patients with sickle cell anemia.[120a] However, the abortion rate varies from 10 to 20% and premature labor is common. The fertility index is evidently not affected. The incidence of toxemia, stillbirth, cardiac failure, intercurrent respiratory and urinary infections, thrombotic phenomena, and shock is increased.[120a] The maternal mortality rate has been reported as 15%[120a] due to such complications as placenta accreta.[120b]

Cardiac failure, retarded growth,[459] pulmonary tuberculosis,[442] and priapism[460] are also increased. The incidence of amorphous splenic calcifications is 10%.[459] Patients with chronic sickle cell anemia usually have a relatively small spleen. Splenomegaly occurred in 9 of Lichtman's 79 patients.[461] His studies also indicate the possibility of an additional element of blood destruction by the spleen, i. e., hypersplenism.

There is no clinical correlation between the sickling phenomenon and the incidence of frostbite.[462]

(*b*) Thalassemia. Complications in three siblings in the fourth and fifth decades of life included leg ulcers, urate calculi, and gouty arthritis.[463] Pleuro-

455. Chernoff, A. I.: Immunologic Studies of Fetal Hemoglobin, abstracted, J. Lab. & Clin. Med. **40**:787, 1952. Itano.[21a]

456. Singer, K., and Chernoff, A. I.: Studies on Abnormal Hemoglobins: III. The Interrelationship of Type S (Sickle Cell) Hemoglobin and Type F (Alkali Resistant) Hemoglobin in Sickle Cell Anemia, Blood **7**:47, 1952.

457. Branson, H., and Banks, L. O.: The Turnover Time of Phosphorus in Normal, Sickle Cell Trait, and Sickle Cell Anemia Blood in Vitro as Measured With P^{32}, Science **115**:89, 1952.

458. Tosteson, D. C.; Shea, E., and Darling, R. C.: Potassium and Sodium of Red Blood Cells in Sickle Cell Anemia, J. Clin. Invest. **31**:406, 1952.

459. Ehrenpreis, B., and Schwinger, H. N.: Sickle Cell Anemia, Am. J. Roentgenol. **68**:28, 1952.

460. Chandler, B. F., and Kehoe, E. L.: Priapism in Sickle Cell Anemia, U. S. Armed Forces M. J. **3**:1699, 1952.

461. Lichtman, H., and Shapiro, H.: Splenic Hyperfunction in Sickle Cell Anemia, Proceedings, American Federation Clinical Research, National Meeting, Atlantic City, N. J., May 4, 1952.

462. Ellenhorn, M. J., and Weiner, D.: Sickle Cell Trait and Frostbite, U. S. Armed Forces M. J. **3**:1845, 1952.

463. March, H. W.; Schlyen, S. M., and Schwartz, S. E.: Mediterranean Hemopathic Syndromes (Cooley's Anemia) in Adults, Am. J. Med. **8**:46, 1952.

pericarditis in one patient responded to cortisone. Exogenous hemochromatosis, attributed to multiple blood transfusions, was seen in a patient who had received 76,665 cc. of blood over a period of nine years.[464]

Erythroblastosis fetalis. A number of reviews of erythroblastosis fetalis cover the frequency factors involved, treatment, and complications.[465] The clinical significance and application of anti-Rh antibody determinations have been discussed.[466] Wiener [118b] has asserted that a definite correlation exists between the maternal antibody titer and the severity of the baby's illness. Controversy continues on the occurrence of an anamnestic type of rise in anti-Rh antibody titer when the fetus is negative.[118b,c]

The antibody titer in the sera of infants' cords serves as a better diagnostic criterion than maternal antibody titer at delivery.[118d] Others consider that the concentrations of nonhematin iron and urobilinogen in amniotic fluid taken at various times during pregnancy offers a reliable guide for fetal prognosis.[118e] Diagnostic and clinical significance has been also attached to intravascular red cell aggregation observed in the conjunctival vessels of erythroblastotic infants.[467] Kernicterus is likely to occur in babies with serum bilirubin levels above 30 mg. and is unlikely to occur when the level remains below 20 mg. per 100 cc.[468] The presence of cold hemagglutinins in maternal serum has little or no bearing on the condition of the baby.[469]

Sensitization to rh″ and hr′ factors has occurred in several instances.[470] A variant of the D antigen was detected in three Australian aborigines.[471] Immu-

464. Frumin, A. M.; Waldman, S., and Morris, P. M.: Exogenous Hemochromatosis in Mediterranean Anemia, Pediatrics **9**:290, 1952.

465. (*a*) Mengert, W. F.: Erythroblastosis Fetalis (Hemolytic Disease of the Newborn), Arkansas M. Soc. **48**:193, 1952. (*b*) Tieche, H. L.: Erythroblastosis Fetalis, West. J. Surg. **60**:280, 1952. (*c*) Cross, A. R.: The Rh Factor and Erythroblastosis Fetalis, North Carolina M. J. **12**:426, 1951. (*d*) Newman, W.: Erythroblastosis Among Negroids, correspondence, J. A. M. A. **150**:1444, 1952. (*e*) Davidsohn, I.: Serologic Aspects of the Rh Factor, Chicago M. School Quart. **12**:127, 1951. (*f*) Ratnoff, O. D.; Lauster, C. F.; Sholl, J. G., and Schilling, M. O.: A Hemorrhagic State During Pregnancy With the Presence of Maternal Rh Antibodies, Death of the Fetus and Hypofibrinogenemia, Am. J. Med. **8**:3, 1952. (*g*) Snelling, C. E.; Donohue, W. L., and McKee, M.: Management of Erythroblastosis Fetalis, Canad. M. A. J. **66**:356, 1952.

466. Walker, W.: Hemolytic Disease of the Newborn, Brit. M. J. **1**:108, 1952. Bond, Knowles, and Engelfried.[118c] Kelsall and Vos.[118d]

467. Zilliacus, H., and Arajarvi, T.: Intravascular Red Cell Aggregation in Erythroblastosis Foetalis, Acta pædiat. **41**:267, 1952.

468. Hsia, D. Y.; Allen, F. H., Jr.; Gellis, S. S., and Diamond, L. K.: Erythroblastosis Fetalis: VIII. Studies of Serum Bilirubin in Relation to Kernicterus, New England J. Med. **247**:668, 1952.

469. Abt, E. G., and Orth, G. W.: Blutgruppenantikörper und Kälteantikörper bei Neugeborenengelbsucht, Arch. Gynäk. **181**:638, 1952.

470. Wiener, A. S., and Brancato, G. J.: Problems in the Management of Erythroblastosis Fetalis, with 5 Examples Exhibiting Unusual Serological Findings, J. Lab. & Clin. Med. **40**:27, 1952. Dunne, C. J., Jr., and Innella, F. P.: Dual Sensitization to the rh″ (E) and hr′ (c) Factors Detected Ante-Natally, Blood **7**:526, 1952.

471. Walsh, R. J.: Variants of the Blood Group Gene D in 2 Native Races, M. J. Australia **2**:405, 1952.

nization of pregnant mothers to A, B, or S antigens has resulted in several cases of erythroblastosis.[472] The frequency of isoimmunization during pregnancy was 4.8% in 1,000 unselected deliveries.[1188]

Diagnosis of the Clinical Hemolytic Syndromes: The hemolytic syndromes are due to such a wide variety of factors that diagnosis at times may be difficult. The techniques in the past ten years have resulted in development and refinement of more precise diagnoses. A flow diagram of a practical laboratory approach to the differentiation of the majority of hemolytic syndromes is presented in Figure 3.[473] Our hypothesis assumes that the history, the peripheral blood (Fig. 3 *I*), and the marrow (Fig. 3 *II*) do not reveal the specific diagnosis but do indicate a hemolytic process. So one proceeds with (Fig. 3 *III*) the osmotic fragilities. Thalassemia, sicklemia, and iron-deficient red cells show decreased osmotic fragilities. Hereditary spherocytosis and acquired hemolytic anemia, on the other hand, show increased osmotic fragilities; however, at this stage, these are not differentiated from each other. One continues with the incubated osmotic fragility (red cells from defibrinated blood, incubated at 37 C. for 24 hours, and tested in a hypotonic system). The cells from hereditary spherocytosis show a marked increase in fragility (broken line). The cells of acquired hemolytic anemia show less change but generally assume an asymmetrical type of hemolytic curve, which may cross over the normal control or that of the preincubated specimen (dotted line). In the test of incubated mechanical fragilities cells from hereditary spherocytosis show a marked increase (3+) after incubation and cells of acquired hemolytic anemia show only a moderate increase (1+).

If the diagnosis is still not evident, one continues with the immunologic tests as follows (Fig. 3 *IV*):

1. Examination for incomplete antibodies is made with (*a*) the trypsin-red-blood-cell test,[397] which detects incomplete antibodies in the serum, and (*b*) the anti-human-globulin test (Coombs), which detects antibodies on the red cell.[397] These tests are positive in 80% of the acquired hemolytic anemias. The presence of incomplete antibodies has been suggested as means of differentiating acquired hemolytic anemia from hereditary spherocytosis. In up to one-third of hereditary spherocytoses there may be incomplete antibodies, and they are occasionally present in thalassemia and sicklemia.[397] These tests are not specific in the differential diagnosis of these entities but contribute to the accumulated evidence in establishing the diagnosis.

2. Paroxysmal cold hemoglobinuria of the cold agglutinin type is diagnosed by the presence of these antibodies in significant titers.[474]

3. Cold hemolysins associated with syphilis establish paroxysmal cold hemoglobinuria by the presumptive and complete Donath-Landsteiner tests.[475] Acid hemolysins of paroxysmal nocturnal hemoglobinuria are demonstrable with the screening and acid-serum (Ham) tests.[475]

472. Levine, P.; Ferraro, L. R., and Koch, E.: Hemolytic Disease of the Newborn Due to Anti-S, Blood **7**:1030, 1952. Footnote 167.

473. The illustration is of the routine of the hematology division of Ohio State University.

474. Bouroncle, B. A.; Dodd, M. C., and Wright, C. S.: A Study of Cold Hemagglutinins for Normal and Trypsinized Red Blood Cells in the Serum of Normal Individuals and of Hemolytic Anemias, J. Immunol. **67**:265, 1951.

475. Ham, T. H.: A Syllabus of Laboratory Examinations in Clinical Diagnosis, Cambridge, Mass., Harvard University Press, 1950.

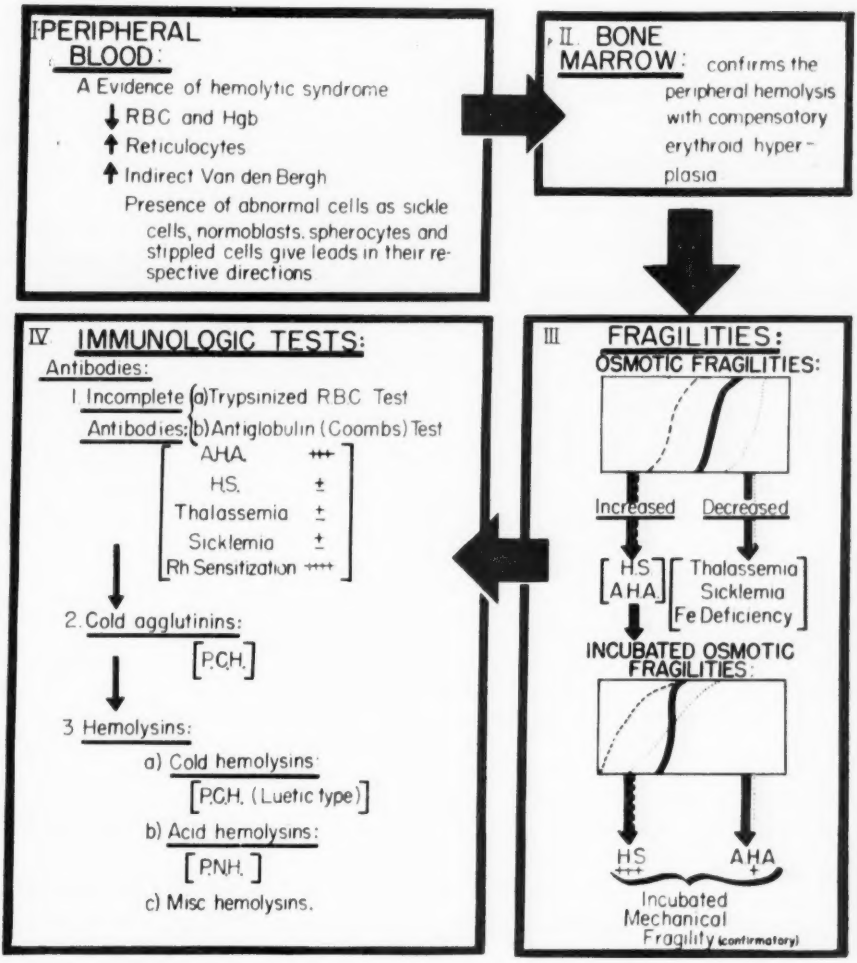

Fig. 3.—A flow diagram of a practical laboratory approach to the differentiation of the majority of the hemolytic syndromes. The hypothesis assumes that the history, the peripheral blood (*I*), and the marrow (*II*) do not indicate the specific diagnosis but do indicate a hemolytic process. The osmotic fragilities (*III*) differentiate hereditary spherocytosis (H. S.) and acquired hemolytic anemia (A. H. A.) from thalassemia, sicklemia, and iron deficiency anemias. The incubated osmotic and mechanical fragilities further differentiate hereditary spherocytosis (H. A.) and acquired hemolytic anemia (A. H. A.). If the diagnosis is still not evident, one proceeds with the immunologic tests (*IV*). The presence of incomplete antibodies is not specific in the differential diagnosis but contributes to the accumulated evidence in establishing the diagnosis. Search for cold agglutinins and cold, acid, and miscellaneous hemolysins is continued if indicated.

The flow diagram is a working outline and does not include hemolytic syndromes associated with infectious, chemical, and physical agents; transfusion incompatabilities, and march hemoglobinuria. No test is 100% efficient. Occasionally diagnsis must depend on correlation of a number of the tests and the clinical picture.

Therapy of the Hemolytic Anemias: Corticotropin and cortisone attenuate the hemolysis in a number of instances of acquired hemolytic anemia, thalassemia, and sickle cell anemia.[476] Compound F acetate also appears to be of value in acquired hemolytic anemia.[108f] There are occasional failures.[109] Hormonal therapy previous to splenectomy has been used with some success.[477]

Corticotropin in paroxysmal nocturnal hemoglobinuria is ineffective.[478]

The use of corticotropin and cortisone in an attempt to alter the Rh antibody titer during pregnancy and their effect in the newborn are considered inconclusive by one worker,[112c] although other investigators are more optimistic.[112a,b]

Therapy directed to the spleen in secondary hemolytic anemia is effective if the destruction is primarily splenic. For instance, in a hemolytic anemia associated with kala-azar [416] treatment with hydroxystilbamidine results in marked reduction of splenic size with gradual improvement of the hemolytic anemia. In the idiopathic or secondary types splenectomy may be ineffective if the red cell destruction is massively taking place throughout the entire reticuloendothelial system. Therefore, elimination of the fraction of splenic destruction is not sufficient to adequately reequilibrate the production vs. destruction balance.

Treatment of idiopathic acquired hemolytic anemia [479] with splenectomy has been the stand-by for many years. In hereditary spherocytosis removal of all splenic tissue corrects the excessive hemolysis in 95% of the cases.

Splenectomy is contraindicated in hemolytic anemia developing secondarily to splenic myeloid metaplasia with inadequate marrow production.[419]

Splenectomy is of variable benefit in patients with paroxysmal nocturnal hemoglobinuria [480] and causes no improvement in patients with microdrepanocytic disease.[21b] Splenectomy was of some benefit in two Chinese siblings with thalassemia.[481]

A number of reports confirm the higher survival rate with exchange transfusions in erythroblastotic infants.[482]

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476. (*a*) Girdwood, R. H.: Some Problems of the Hemolytic Anemias, Practitioner **168**: 249, 1952. (*b*) Hansen, K. B., and Andersen, J.: Blood Changes in Hemolytic Anemia under ACTH Therapy, Blood **7**:1210, 1952. (*c*) Hansen, K. B.: Effect of ACTH on Hemolytic Anemia, Lancet **1**:419, 1952. (*d*) Sass, M.: ACTH and Cortisone in the Treatment of Sickle-Cell Anemia, New England J. Med. **246**:583, 1952. (*e*) Footnote 108*d*, *e*, and *g*. (*f*) Englert and Warshaw.[111] (*g*) Sacks, Workman, and Jahn.[414] (*h*) Dubois.[417]

477. Saint and Gardner.[108d] Girdwood.[476a]

478. Kalant, N., and Cyr, D. P.: Treatment of Paroxysmal Nocturnal Hemoglobinuria with ACTH, Blood **7**:607, 1952. Girdwood.[476a]

479. Footnote 108*d* and *e*. Englert and Warshaw.[111] Sacks, Workman, and Jahn.[414] Dubois.[417]

480. Andersson, B.: A Splenectomized Case of Paroxysmal Nocturnal Hemoglobinuria, Acta med. scandinav. **143**:197, 1952. Letman.[428]

481. Shapiro, I.; Schneck, H., and Etess, A. D.: Splenectomy in 2 Chinese Siblings with Mediterranean Anemia, New York J. Med. **52**:1426, 1952.

482. Mollison, P. L., and Walker, W.: The Treatment of Haemolytic Disease of the Newborn, Lancet **1**:429, 1952. Kelsall and Vos.[118d] Ticche.[465b] Snelling, Donohue, and McKee.[465g] Hsia.[468]

The therapeutic value of the Rh hapten is questioned.[483] Premature delivery of the erythroblastotic baby is sharply criticized and discouraged.[483]

The Rarer Anemic States.—It is considered that uremia may be the cause of some of the unexplained anemias.[484] At times the toxic effect in uremia is not confined to erythroid depression alone but involves a general marrow hypoplasia.[485] The discussion of hypoplastic anemias is made on page 363.

Four cases of the congenital Fanconi syndrome illustrate the pancytopenia accompanied by varied developmental anomalies (i. e., pigmentation, vitiligo, microphthalmia, strabismus and papilledema, microcephaly, and a delay in the appearance of the carpal centers and a double nucleus in the tarsal scaphoid). The pancytopenia was due to marrow hypoplasia.[486]

Five cases of erythremic myelosis (Di Guglielmo's disease) were characterized by chronic refractory anemia, enlargement of the liver and spleen, and highly active erythropoiesis with marked maturation arrest in the marrow.[487]

The "spurious," "erroneous," or "relative" anemias are discussed in the following section.

Abnormalities in the Circulating Red Cell Mass and Plasma

Refinement, availability, and popularity of two groups of techniques have resulted in a clearer understanding of abnormalities in the circulating red cell mass and/or plasma. First, erythrocyte production has been estimated by measuring radioactive iron turnover during a prescribed interval. The second group of techniques [12a] provides more exact estimation of the circulating red cell mass (radioactive iron [12c,d] [Fe^{55}; Fe^{59}], chromium [12e] [Cr^{51}], and potassium [12f] [K^{42}]) and the circulating plasma (Congo red, Evans blue [T-1824], or I^{131}-tagged serum albumin).

Polycythemia.—Although polycythemia vera is characterized by a triune marrow hyperplasia, i. e., an increase of erythroid, myeloid, and platelet production, there are occasional cases that exhibit minimal evidence of myeloid increase.[488]

The reason for the unrestrained production of all marrow elements is unknown. However, Lawrence and co-workers [489] have studied plasma iron turnover in primary and secondary polycythemia before and after one to three days of oxygen administration. Oxygen diminishes red cell production in secondary polycythemia

483. Dippel, L.: The Prevention of Erythroblastosis Fetalis by the Use of Rh Hapten, South. M. J. **45**:954, 1952.

484. Alder, A.: Die Urämie als Ursache ungeklärter Anämien und Myelopathien, Deutsche med. Wchnschr. **77**:536, 1952.

485. Levin, W. C., and Gregory, L.: Hematological Effects of Uremia, South. M. J. **45**:121, 1952.

486. Reinhold, J. D. L.; Neumark, E.; Lightwood, R., and Carter, C. O.: Familial Hypoplastic Anemia with Congenital Abnormalities (Fanconi's Syndrome), Blood **7**:915, 1952. Sturgis.[263a]

487. Schwartz, S. O., and Critchlow, J.: Erythremic Myelosis (di Guglielmo's Disease): Critical Review with Report of 4 Cases, and Comments on Erythroleukemia, Blood **7**:765, 1952. Mackenzie, I., and Stephenson, A. G.: A Case of Erythremic Myelosis (Di Guglielmo's Anemia): Case Report, ibid **7**:927, 1952.

488. Stroebel, C. F.: Current Concepts of Polycythemia, Proc. Staff Meet., Mayo Clin. **27**:282, 1952.

489. Lawrence, J. H.; Elmlinger, P. J., and Fulton, G.: Oxygen and the Control of Red Cell Production in Primary and Secondary Polycythemia: Effects on the Iron Turnover Patterns with Fe^{59} as Tracer, Cardiologia **21**:337, 1952.

but not in polycythemia vera. It is deduced that the secondary type is under control of normal physiologic mechanisms, while the vera type is neoplastic in nature. An interesting relation has been noted in a case of pernicious anemia which was superseded by polycythemia vera.[208] It is interpreted that the basic "polycythemic" stimulus for overproduction is overshadowed by the diminution in the nutrient factor involved in pernicious anemia. The polycythemia can only emerge after the pernicious anemia is treated. The relation of an artificially induced myxedema and polycythemia vera was observed in a woman over a 17-year period. The myxedema apparently kept the polycythemia in check.[490]

The diagnosis of polycythemia vera is made on (1) the peripheral elevation of the red cells, granulocytes, and platelets, (2) a marked diminution in the sedimentation rate (interpreted as a depressed fibrinogen content of the plasma), (3) normal arterial oxygen saturation, and (4) an increased circulating red cell mass determined by one of the methods mentioned above. Wasserman and co-workers[491] assert that the marrow is of little diagnostic value. However, Block and Bethard[492] note a characteristic pattern of densely cellular marrow with clumps of stem cells and basophilic erythroblasts, little or no iron, and a normal cell distribution, except for slight erythroblastic hyperplasia. These are readily differentiated from marrows of persons with secondary polycythemia.

Effective therapy is dependent on keeping in mind the potential complications. The two most frequent are the two extremes of the coagulation phenomenon: first, intravascular thrombosis, and second, hemorrhage. To prevent the former, control of the increased platelet production is as important as control of the red cells. The impeded hepatic circulation is manifested by low prothrombin and fibrinogen levels. The hypoprothrombinemia is occasionally the cause of serious hemorrhage.

With therapy the fall in blood volume follows two patterns: (1) a decrease in the total red cell volume and plasma volume, resulting in a decreased total blood volume, and (2) a decrease in the total red cell volume and a rise in the plasma volume. This causes decreased total blood volume. No simple or constant relation can be noted between blood volume changes and the rise or fall in blood pressure.[493]

In 12% of patients with polycythemia vera chronic myeloid leukemia or myelofibrosis with myeloid metaplasia eventually develops.[488] Whether the myelosclerosis follows as a natural sequence in the disease process or whether it is due to the effect of therapy is not known.[494] Acute leukemia has been observed in a few patients

490. Limarzi, L. R.; Paul, J. T., and Seed, L.: A Seventeen-Year Follow-Up Study on the Clinical and Hematologic Results of Total Thyroidectomy in a Case of Polycythemia Vera, J. Lab. & Clin. Med. **40**:919, 1952.

491. Wasserman, L. R.; Lawrence, J. H.; Berlin, N. I.; Dobson, R. L., and Estren, S.: The Bone Marrow Picture in Polycythemia Vera Before and After Treatment with Radioactive Phosphorus, Acta med. scandinav. **143**:442, 1952.

492. Block, M., and Bethard, W.: Bone Marrow Studies in Polycythemia, J. Clin. Invest. **31**:618, 1952.

493. Prentice, T. C.; Berlin, N. I., and Lawrence, J. H.: Effect of Therapy on Blood Volume, Blood Pressure, and Spleen Size in Polycythemia Vera, A. M. A. Arch. Int. Med. **89**:584, 1952.

494. Marson, F. G., and Meynell, M. J.: Polycythemia and Myelosclerosis, Brit. M. J. **1**:1113, 1952.

subjected to total body irradiation with either radioactive phosphorus or with roentgen radiation over a number of years.[488] This is a rare complication and is a calculated risk which is far overweighed by the beneficial aspects of this therapy.

The therapy of polycythemia vera is discussed on page 429 in conjunction with the therapy of the leukemias.

Secondary polycythemia is associated with conditions causing chronic anoxia, such as living at high altitudes [495] and lung and heart diseases. The polycythemia secondary to brain tumors is assertedly due to hypoxia resulting from pressure by the tumor on the medullary respiratory center.[496]

Experimental polycythemia has been induced in dogs by hypoxia (equivalent to 20,000 ft. [6,000 meters] altitude). An increase in the daily bile pigment excretion (collected via bile fistula) accompanies the increased erythropoiesis of the first weeks of altitude exposure. The life span of red cells during altitude studies has been found to be about 115 days. Normalization of the polycythemic blood levels takes about six to eight weeks after return to ground level and is achieved by a combined effect of depressed erythropoiesis and increased red cell destruction.[497] Observations in Uludag [498] (1,850 meters) show approximately 10% increase in the erythrocyte count and 9% increase in the hemoglobin concentration by the 10th day at the elevated level. There is a return to normal values within 8 to 10 days after the descent to sea level. Similar findings have been made in the Peruvian Andes.[499] Also, 10 days after descent from 14,900 ft. (4,470 meters) the iron turnover in the Peruvian Indian decreases to one-tenth that observed in his habitat. This approaches that seen in aplastic anemia. There is no evidence for an increased incidence of polycythemia vera among those living at high altitudes.[499]

The therapy in the secondary polycythemias is directed to the primary cause.

"Spurious," "Erroneous," "Relative," or "Apparent" Anemias and Polycythemias.—Wiseman points out [12a] that hemodilution and hemoconcentration may occur both physiologically and pathologically. The result may be an apparent anemia or polycythemia. Both require identification and this is accomplished by determining the total circulating red cell mass. In the "physiologic anemia" in pregnancy, certain instances of "anemia" of leukemia, portal cirrhosis, and cancer the circulating red cell masses have been normal.[12a] A secondary polycythemia associated with alcoholic cirrhosis improved with therapy directed to the cirrhosis; this also was likely a hemoconcentration effect.[500]

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495. Das Gupta, C. R.: Blood Picture of Indians at High Altitude, Indian M. Gaz. **87**:95, 1952.

496. Holmes, C. R.; Kredel, F. E., and Hanna, C. B.: Polycythemia Secondary to Brain Tumor, South. M. J. **45**:967, 1952.

497. Reissmann, K. R.; Burkhardt, W. L., and Hoelscher, B.: Blood Destruction in the Polycythemia Induced by Hypoxia, Blood **7**:337, 1952.

498. Terzioglu, M.; Peköz, N.; Özer, F., and Songar, A.: Studies in Blood Physiology at Mid-Altitude: I. Variations in Blood Morphology at Uludag (1850 m.), Arch. internat. physiol. **60**:233, 1952.

499. Lawrence, J. H.; Huff, R. L.; Siri, W.; Wasserman, L. R., and Hennessy, T. G.: A Physiological Study in the Peruvian Andes, Acta med. scandinav. **142**:117, 1952.

500. Greer, E.: Alcoholic Cirrhosis Simulating Idiopathic Polycythemia Vera, Illinois M. J. **100**:272, 1952.

Wilson and Boyle [12b] have made a thorough study of these "erroneous" anemias and polycythemias and have emphasized that in many anemias of neurasthenia there is a normal circulating red cell mass. "Their notorious failure to respond to antianemic therapy is not surprising." On the other hand, Lawrence and Berlin stress a psychiatric background, with associated undue nervous stress and strain as a factor in producing hemoconcentration with a normal circulating red cell mass, resulting in a "relative" polycythemia.[501]

WHITE BLOOD CELLS

General Physical and Chemical Observations on Leucocytes

Disagreement as to the life span of granulocytes, lymphocytes, and monocytes continues. The life span of 12.8 days as the average is reported for all white blood cell types.[502]

Studies on regulatory mechanisms of circulating leucocytes have been correlated with respiration.[503] During inspiration the arterial leucocyte count falls and the simultaneous venous count rises; reciprocal changes occur on expiration. This is attributed to a tidal ebb and flow of leucocytes into and from the pulmonary circulation. This "reservoir" of leucocytes and platelets in the pulmonary circulation is discharged into the circulation by epinephrine stimulation.[504] Histamine given intravenously was followed by an arterial leucopenia within 30 seconds, persisting from one to three minutes.[505]

Leucocytes released as a result of accelerated leucopoiesis show increased stickiness and activity.[506] The leucocytosis that is associated with epinephrine and arterenol (norepinephrine) is not related to the resulting increase in blood pressure.[507] Leucocytosis is produced in rabbits by a vitamin E deficient diet.[508] The lysozyme-like enzyme in human leucocytes has received attention in three publications.[509] An in vitro method has been described for determining the adverse effect

501. Lawrence, J. H., and Berlin, N. I.: Relative Polycythemia—The Polycythemia of Stress, Yale J. Biol. & Med. **24**:498, 1952.

502. Kline, D. L., and Cliffton, E. E.: The Life Span of Leucocytes in the Human, Science **115**:9, 1952.

503. Bierman, H. R.; Kelly, K. H.; Cordes, F. L.; Petrakis, N. L.; Kass, H., and Shpil, E. L.: The Influence of Respiratory Movements upon the Circulating Leukocytes, Blood **7**:533, 1952.

504. Bierman, H. R.; Kelly, K. H.; Cordes, F. L.; Byron, R. L., Jr.; Polhemus, J. A., and Rappoport, S.: The Release of Leukocytes and Platelets from the Pulmonary Circulation by Epinephrine, Blood **7**:683, 1952.

505. Bierman, H. R.; Kelly, K. H.; Cordes, F. L.; White, L. P., and Littman, A.: The Hematological Response of Leukemic and Non-Leukemic Patients to Intravenous Histamine, Cancer Res. **12**:248, 1952.

506. Fleck, L.: Über Leukergie, Acta haemat. **8**:282, 1952.

507. Credner, K., and Krüger, K.: Untersuchungen über die durch Adrenalin und Noradrenalin verursachte Leukocytose und ihre Beeinflussung durch Opilon, Arch. exper. Path. u. Pharmakol. **216**:310, 1952.

508. Dinning, J. S.: Leucocytosis in Vitamin E Deficient Rabbits, Proc. Soc. Exper. Biol. & Med. **79**:231, 1952.

509. Kerby, G. P.: The Effect of Various Bacterial Derivatives and of Physical Injury on the Lysozyme-Like Activity of Human Leucocytes, abstracted, J. Clin. Invest. **31**:643, 1952. Kerby, G. P.: Release of Enzyme from Human Leukocytes on Damage by Bacterial Derivatives, Proc. Soc. Exper. Biol. & Med. **81**:381, 1952. Hiatt, R. B.; Engle, C.; Flood, C., and Karush, A.: The Role of the Granulocyte as a Source of Lysozyme in Ulcerative Colitis, J. Clin. Invest. **31**:721, 1952.

of various bacterial derivatives on human leucocytes by measuring the released lysozyme-like enzyme. The increased lysozyme titer in the stools of patients with ulcerative colitis is due to destruction of the invading granulocytes. An attempt has been made to determine the activity of nucleotidase in the various types of leucocytes.[510]

When the adrenal is stimulated, a resulting humoral factor promotes phagocytosis.[511] The phagocytosis of neutrophilic leucocytes is also increased by estrone and small doses of diethylstilbestrol.[512] A phagocytosis inhibition test has been described for infection hypersensitivity, useful for in vitro evaluation of infection allergy.[513]

Lawrence and co-workers [426] have reviewed the white blood cell changes in various clinical states as well as the associated histochemical changes.

L. E. Cell Phenomenon

Since the original description of the L. E. cell phenomenon, many techniques for its demonstration have been reported and confirmed. A "two hour blood clot technique," containing the three elements necessary for the phenomenon (i. e., lytic factor, nuclear proteins, and viable leucocytes) greatly enhances its occurrence.[514]

Hargraves [126] has stressed the fact that the L. E. cell phenomenon is an in vitro occurrence and therefore may be an artifact, though nonetheless a "specific" one. He suggested the possibility that blood platelets, or their disintegration products, constitute a source of the undefined factor responsible for producing the phenomenon in vitro and based his conjecture on the following observations: (1) the greatest number of L. E. cells invariably occur in the "fringe" areas of the preparations, where the platelets are in the greatest number; (2) there is a tremendous exacerbation of the L. E. phenomenon in preparations in which platelets are allowed to disintegrate; (3) clinically, lupus erythematosus seems to "flare" with relation to menses, pregnancies, surgical procedures, and other conditions where platelet disintegration is involved.

Three methods of experimental stimulation of the L. E. phenomenon have been reported: (1) the use of leucocytic debris on which glycogen has been absorbed; (2) addition of starch granules to which leucocytes are attracted with subsequent formation of rosettes; (3) addition of trypsin to normal blood, resulting in the liberation of nuclear masses around the periphery of which leucocytes adhere.[515]

510. Swendseid, M. E.; Wright, P. D., and Bethell, F. H.: Variations in Nucleotidase Activity of Leucocytes: Studies with Leukemia Patients, J. Lab. & Clin. Med. **60**:515, 1952.

511. Ludány, G.; Vajda, J., and Backhausz, R.: Vagoinsulares System und die Phagozytose der Leukozyten, Arch. Internat. pharmacodyn. **89**:269, 1952.

512. Burger, H., and Leonhardt, K.: Über die Beeinflussung der Leukocytenphagocytose durch die weiblichen Sexualhormone in Vitro (Zugleich ein Beitrag über den Angriffspunkt der weiblichen Sexualhormone im Stoffwechsel), Arch. Gynäk. **181**:300, 1952.

513. Merchant, D. J., and Chamberlain, R. E.: A Phagocytosis Inhibition Test in Infection Hypersensitivity, Proc. Soc. Exper. Biol. & Med. **80**:69, 1952.

514. Zimmer, F. E., and Hargraves, M. M.: The Effect of Blood Coagulation on L. E. Cell Formation, Proc. Staff Meet., Mayo Clin. **27**:424, 1952.

515. Silver, H., and Kuna, A.: Experimental Simulation of the L. E. Phenomenon, J. Invest. Dermat. **19**:281, 1952.

Deoxyribonuclease inhibitor is found in extracts of normal human white blood cells.[516] When this inhibitor is removed, the washed leucocytes are more sensitive to the L. E. phenomenon. Suppression of this effect is demonstrated by recombining the active inhibitor with the system.

The L. E. phenomenon persists in remission of acute lupus erythematosus.[517]

The "specificity" of the L. E. phenomenon is questioned by Walsh and Zimmerman, who found it present in four cases of severe penicillin hypersensitivity and in one case of serum sickness.[518]

Infectious Mononucleosis and Acute Infectious Lymphocytosis

Infectious Mononucleosis.—The history, incidence, and clinical picture of infectious mononucleosis has been reviewed.[519] A rapid slide test for detection of heterophile antibodies has been described.[520] The incidence of false-positive serological tests for syphilis in infectious mononucleosis depends on the test method employed.[521] Occasionally the heterophile develops very slowly.[522] Differential absorption tests are sometimes necessary.[523] Cold agglutinins for sheep cells cause an occasional false-positive test.[524] This error is eliminated by rewarming the test serum-cell mixtures following the usual overnight refrigeration.

The types of lymphocytes of infectious mononucleosis bear no relationship to the clinical course, although Type III lymphocytes and granulocytic immaturity are more frequently seen when the onset is acute. Toxic changes in the granulocytes are correlated with a severe clinical course.[525]

Infectious mononucleosis has been manifested by clinical epilepsy,[526] meningitis,[527] and the Guillain-Barré syndrome.[528] It is often associated with hepatitis.

516. Kurnick, N. B.; Schwartz, L.; Pariser, S.; Lee, S., and Irvine, W.: The Role of Desoxyribonuclease and a Nuclease Inhibitor from Leucocytes in the Lupus Erythematosus Cell Phenomenon, J. Clin. Invest. **31**:645, 1952.

517. Bonnin, J. A.: L. E. Cells in the Peripheral Blood: With a Report of a Case of Acute Disseminated Lupus Erythematosus, M. J. Australia **1**:672, 1952.

518. Walsh, J. R., and Zimmerman, H. J.: Demonstration of the "L. E." Phenomenon in Penicillin Hypersensitivity and Serum Sickness, Proceedings, American Federation Clinical Research, Midwest Section, Chicago, Nov. 6, 1952.

519. Davidsohn, I.: Infectious Mononucleosis, Chicago M. School Quart. **4**:13, 1952.

520. Glassey, F. J.: Evaluation of the Rapid Heterophile Antibody Slide Test, U. S. Armed Forces M. J. **3**:947, 1952.

521. Zarafonetis, C. J. D., and Kent, J. F.: Serologic Tests for Syphilis in Infectious Mononucleosis, abstracted, J. Lab. & Clin. Med. **40**:965, 1952.

522. Bakst, H., and Leibowitz, S.: Infectious Mononucleosis: Report of Case with First Appearance of Significant Numbers of Heterophil Antibodies and Abnormal Lymphocytes ("Virocytes") in Seventh Week of Illness, Am. J. Med. **13**:235, 1952.

523. Leibowitz, S.: Infectious Mononucleosis: The Value of Differential Absorption Tests in its Serologic Diagnosis, Am. J. Med. **13**:172, 1952.

524. Zarafonetis, C. J.; Oster, H. L., and Colville, V. F.: Cold Agglutination of Sheep Erythrocytes as a Factor in False-Positive Heterophile Agglutination Tests, abstracted, J. Lab. & Clin. Med. **40**:964, 1952.

525. Stevens, J. E.; Bayrd, E. D., and Heck, F. J.: Infectious Mononucleosis: The Prognostic Significance of Various Changes of the Blood Leukocytes, Blood **7**:31, 1952.

526. Bercel, N. A.: Infectious Mononucleosis, Encephalitis, Epilepsy, Am. J. M. Sc. **224**:667, 1952.

527. Kalk, K., and Ulbricht, J.: Über eine neurologische Komplication bei der infectiösen Mononukleose, Deutsche med. Wchnschr. **77**:397, 1952.

528. Nixon, R. K., Jr.: Infectious Mononucleosis and the Guillain Barre Syndrome: A Review of the Literature and the Report of 2 Cases, Illinois M. J. **102**:316, 1952.

Liver biopsies show findings similar to those in epidemic hepatitis. The peak of degenerative and regenerative activity is reached between the 10th and the 30th day. During this period the peripheral infiltration and Kupffer cell activity are most pronounced.[529] A fatal case was due to renal and liver failure.[530] Other complications include hemolytic anemia[531] and purpura,[532] both of which may be expressions of secondary hypersplenism.

Although 50% of 51 patients treated with penicillin or aureomycin showed prompt improvement, comparison with a control group indicated no reduction in the average duration of symptoms or fever.[533]

Acute Infectious Lymphocytosis.—Acute infectious lymphocytosis is generally manifested by minimal symptoms and signs even though counts of 70,000 or 80,000 cells per cubic centimeter are quite common. The cells are small mature lymphocytes. Several epidemics in English children have been reported.[534]

Leucopenia

The granulocytopenias due to toxic bone marrow depression are discussed on page 364.

The term "primary hypoplastic neutropenia" has been suggested for a type of neutropenia characterized by a defect in granulocyte production in the marrow.[535] Splenectomies on three of four patients failed to alter the course of this disease.

A transient neutropenia of 15 minutes' duration follows the administration of nicotinic acid.[536] Leucopenia in rats fed a methionine-deficient basal diet is prevented by supplementation with *p*-dimethylaminoazobenzene plus vitamin B_{12}.[537]

In a case of cyclic neutropenia occurring at 17- to 25-day intervals there was improvement with corticotropin and later with splenectomy.[538] The past literature has been discussed. No entirely satisfactory explanation for these phenomena has been found.

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530. Marshall, S., and Millingen, K. S.: Unusual Features in a Fatal Case of Infectious Mononucleosis, Brit. M. J. **1**:1325, 1952.

531. Mermann, A. C.: Acute Hemolytic Anemia with Infectious Mononucleosis, U. S. Armed Forces M. J. **3**:1551, 1952.

532. Ogilvie, C. M., and Parry, T. E.: Infectious Mononucleosis with Thrombocytopenic Purpura, Brit. M. J. **2**:977, 1952.

533. Schultz, A. L., and Hall, W. H.: Clinical Observations in 100 Cases of Infectious Mononucleosis and the Results of Treatment with Penicillin and Aureomycin, Ann. Int. Med. **36**:1498, 1952.

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535. Spaet, T. H., and Dameshek, W.: Chronic Hypoplastic Neutropenia, Am. J. Med. **8**:35, 1952.

536. Bassen, F. A.; Etess, A. D., and Rosenthal, R. L.: Leukopenia Following Administration of Nicotinic Acid, Blood **7**:623, 1952.

537. Dinning, J. S.; Payne, L. D., and Day, P. L.: Influence of Dimethylaminoazobenzene on Leukocyte Production in the Rat, Blood **7**:376, 1952.

538. Monto, R. W.; Shafer, H. C.; Brennan, M. J., and Rebuck, J. W.: Periodic Neutropenia Treated by Adrenalcorticotrophic Hormone and Splenectomy, New England J. Med. **246**:893, 1952.

LEUKEMIA AND LYMPHOMA

We know little or nothing of the physiology of leukopoiesis, and I am convinced that we shall not understand leukemia until some of these basic physiologic facts have been determined. If half the time and energy which have been devoted to devising and exploiting empirical remedies for the symptomatic treatment of the disease, reducing the leukocyte count, had been expended on basic physiology and pathology, we might well be much nearer to rational treatment. (Sir Lionel Whitby.[539])

Leukemia in the Experimental Animal.—Kirschbaum summarized the status of rodent leukemia as follows:[540]

1. Morphologic types of lymphoblastoma simulating those seen in man appear in rodents.

2. Interaction of genetic and extrinsic factors determine the time of appearance and type of lymphoblastoma. A nongenetic factor contributing towards resistance is transmitted from mother to offspring and may be supplied before birth or by nursing alone. Susceptibility to the development of "spontaneous" leukemia is not determined by genes identical with those involved in reactions to leukemogenic agents such as ionizing radiations, carcinogenic hydrocarbons, and estrogenic hormones. Specific genes may control susceptibility to each leukemogen. Leukemogenic agents may act synergistically in strains of mice susceptible to the independent action of each agent.

3. Leukemic cells of certain transfer lines may harbor a virus which is not an etiologic agent for leukemia, but which causes an illness hastening death from leukemia and alters the antigenicity of cells or the immune reaction of the host. Freezing and lyophilization of mouse leukemic cells render them inactive for transmitting leukemia. [There is much evidence in favor of the view that viruses may be the causative agents in cancer. This has been covered in a thorough review published by the New York Academy of Science.[541] Reference to the original group of papers is suggested. One of the most interesting phases of the virus-cancer relation is reported by Gross.[542] He believes that a virus is the responsible agent for a leukemia in mice which is transmissible by means of cell-free extracts. The theory of "vertical transmission" is proposed. That is, communication of the disease occurs from parent to offspring only. The agent may remain in a latent, inactive form. Owing to unknown influences, it may revert to an active form, usually after the host has passed middle age. Nelson[543] has observed the simultaneous occurrence and vertical transmission of a leukemic condition and a viral acute hepatitis.]

4. Estrogen favors, androgen inhibits leukemogenesis in mice in certain situations. The leukemogenic effects of both x-rays and carcinogenic hydrocarbons may be potentiated by estrogenic hormone.

5. Susceptibility to the development of mouse leukemia may represent a property of the thymus, which serves not only as a primary locus for the development of the disease, but may influence its genesis in some unknown manner.

6. A humoral factor may be involved in the development of x-ray-induced leukemia. Radiation of the thymus alone, or of the whole body except the thymus, did not result in the induction of thymic tumors in animals which develop such neoplasms following whole body radiation. Since shielding of an extremity reduced the incidence of x-ray-induced thymoma, it appears that nonirradiated tissue may inactivate a humoral factor produced by radiation.

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540. Kirschbaum, A.: Rodent Leukemia: Recent Biological Studies, Cancer Res. **11**:741, 1951.

541. Viruses as Causative Agents in Cancer, Ann. New York Acad. Sc. **54**:869, 1952.

542. Transmissible Leukemia in Mice, editorial, J. A. M. A. **148**:746, 1952. Gross, L.: Reported at Second National Cancer Conference, Cincinnati, Ohio, March, 1952. Footnote.[541]

543. Nelson, J. B.: Acute Hepatitis Associated with Mouse Leukemia: I. Pathological Features and Transmission of the Disease, J. Exper. Med. **96**:293, 1952; II. Etiology and Host Range of the Causal Agent in Mice, ibid. **96**:303, 1952.

7. In a strain of mice susceptible to a particular leukemogenic agent, the younger the animal is at the time of exposure, the more the susceptibility is enhanced.

8. Nutritional factors such as caloric restriction or cystine deficiency may delay the development and reduce the incidence of spontaneous or carcinogen-induced leukemia. Pyridoxine or riboflavin deficiency are associated with the inhibition of growth of certain transplanted lymphosarcomas. It has been postulated that guanine is essential for the growth of neoplastic cells and that the growth of certain lymphosarcomas may be inhibited by the administration of 8-azaguanine, a guanine analog. The inhibitory effect of folic acid analogs on transplanted leukemia is attributed to interference with folic acid metabolism resulting in diminished nucleic acid synthesis.

9. Genetic factors control the transplantation of leukemic cells. The malignant transplantable elements are only the lymphoblastic round cells and not mesenchymal stromal elements. Antigen-antibody reactions may be involved in transplantibility, since the gene presumably controls immunologic physiology. Homologous and heterologous immune sera may inactivate leukemia cells in vitro. Cytoplasmic constituents of leukemic cells are more highly antigenic than nuclei. Temporary growth of leukemic cells in foreign strains may be accelerated or inhibited by prior multiple injections of frozen, lyophilized tissue. Heterologous transplantation of leukemic cells can be accomplished by previous radiation of the foreign host, but not by inoculation into the anterior chamber of the eye. Humoral factors passing from normal to radiated rats joined by parabiosis may nullify radiation-induced susceptibility. Immunity towards transplanted leukemia can be passively transferred by inoculation of spleen or liver of immune animals. Resistance to homologous transplantation of leukemic cells may be overcome by inoculation of large doses of cells into very young animals.

10. Various agents may inhibit or delay the growth of certain lines of transplanted leukemic cells. Among these are "radiomimetic drugs," folic acid antagonists, cortical hormones, ionizing radiations, trivalent arsenic, benzene. Although the most active agents are those which have given the most encouraging clinical results, transplanted leukemia as generally used can at most be considered a helpful but not a critical testing medium. Wide variation exists in the response of different lines of leukemic cells to the same agent. Of greatest significance are the studies on refractoriness of leukemic cells and host to drug therapy.

Among the agents reported as affecting mouse leukemia are (*a*) betaine and sodium formate, which cause elevated excretion of creatine by leukemic mice as the result of an increased rate of synthesis [544]; (*b*) *N*-ethylene substituted phosphoramides [545]; (*c*) an ascorbic acid analog, which decreases mortality [422a]; (*d*) estrogenic hormone, methylcholanthrene, and x-ray, which induce leukemia individually and in combination [546]; (*e*) x-ray and cortisone, which make insusceptible strains susceptible to transplanted leukemia [547]; (*f*) diaminodichlorophenyl pyrimidines, which prolong survival time [548]; (*g*) combined radioactive gold and aminop-

544. Dinning, J. S.; Seager, L. D.; Payne, L. D., and Totter, J. R.: The Metabolism of Betaine and Sodium Formate by Leukemic Mice, Science **116**:121, 1952.

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547. Werder, A. A.; Syberton, J. T., and Friedman, J.: The Influence of Roentgen Radiation and Cortisone Upon the Transplantability of Mouse Leukemic Cells Line I_B, Cancer Res. **12**:306, 1952.

548. Burchenal, H.; Goetichius, S. K.; Stock, C. C., and Hitchings, G. H.: Diamino Dichlorophenyl Pyrimidines in Mouse Leukemia, Cancer Res. **12**:251, 1952.

terin, which show a synergic cytotoxic effect[549]; (*h*) 66 substituted hydrazines and related compounds, which have been found to be inactive[550]; (*i*) amethopterin with alien mouse spleen tissue, which delays tumor growth,[551] and (*j*) corticotropin[552] and heparin, which have no effect.[553]

Burchenal and co-workers[554] have used an in vitro technique for inactivating leukemia cells as an aid in differentiating between modes of action of compounds chemotherapeutically active against transplanted mouse leukemia.

Nuclei from spleens of mice with transplanted leukemia contain over four times as much pentosenucleic acid as those from normal spleen; deoxypentosenucleic acid and nitrogen contents are also increased. These differences are similar to those reported for rapidly growing tissue. In spontaneous leukemia there is no increased deoxypentosenucleic acid and nitrogen content and but slight increase in nuclear pentosenucleic acid over the normal.[555]

Observation of Physical and Chemical Aspects of Leukemia.—The rate of formation and the life span of leukocytes have been studied in vitro by incorporation of radioactive phosphorus (P^{32}) into deoxypentosenucleic acid.[556] The life span of cells from chronic granulocytic and subacute monocytic leukemias is about 3 days; for those from chronic lymphatic leukemia, 30 days. In two cases of acute lymphatic leukemia there was a lymphocyte life span of three days. It is suggested that the method may serve as a means of estimating the degree of acuteness. With radioactive zinc[65] the life span of leukemic granulocytes is found to be 15 to 40 hours.[557]

Metabolism: Manometric measurements of aerobic glycolysis have proved unsuitable for determinations of either glucose utilization or lactic acid formation of leukemic white cells.[558] Lactic acid accounts for only 75% of the total acid formed aerobically by myelogenous leukemic leucocytes. Cells from chronic myelogenous leukemias also exhibit greater glucose utilization than those from chronic lymphatic leukemia.

549. Goldie, H.; Watkins, F. B.; Powell, C., and Hahn, P. F.: Effect of Colloidal Au^{198} on the Growth Cycle of Leukemic Cells and on the Survival of Their Host, Cancer Res. **12**:92, 1952.

550. Freedlander, B. L., and Furst, A.: Effect of Substituted Hydrazines and Related Compounds on Myeloid Mouse Leukemia C-1498, Proc. Soc. Exper. Biol. & Med. **81**:638, 1952.

551. Foley, E. J.: Retardation and Regression of Lymphosarcoma in C3H Mice Treated with Alien Mouse Spleen and A-Methopterin, Proc. Soc. Exper. Biol. & Med. **79**:155, 1952.

552. Block, M., and Takano, G.: Effect of ACTH upon Induced Leukemia in DBA Mice, Cancer Res. **12**:250, 1952.

553. Kreisler, L.: Effect of Heparin on the Growth of a Transplantable Lymphosarcoma in Mice, Science **115**:145, 1952.

554. Burchenal, J. H.; Cremer, M. A.; Williams, B. S., and Armstrong, R. A.: Sterilization of Leukemic Cells in Vivo and in Vitro, Cancer Res. **11**:700, 1951.

555. Petermann, M. L., and Schneider, R. N.: Nuclei from Normal and Leukemic Mouse Spleen: The Nucleic Acid Content of Normal and Leukemic Nuclei, Cancer Res. **11**:485, 1951.

556. Osgood, E. E.; Tivey, H.; Davison, K. B.; Seaman, A. J., and Li, J. G.: The Relative Rates of Formation of New Leukocytes in Patients with Acute and Chronic Leukemias: Measured by the Uptake of Radioactive Phosphorus in the Isolated Desoxyribosenucleic Acid, Cancer **5**:331, 1952.

557. Ebaugh, F. G.: The Metabolism of Radioactive Zinc—65 in Patients with Malignant Disease, Proceedings American Federation Clinical Research, National Meeting, Atlantic City, N. J., May 4, 1952.

558. Bird, R. M.; Clements, J. A., and Becker, L. M.: The Metabolism of Leukocytes Taken from Peripheral Blood of Leukemic Patients, Cancer **6**:1009, 1951.

Oxygen and glucose consumption and lactic acid formation are greater in normal leucocytes than in those from chronic myelocytic and chronic lymphatic leukemia.[559] The effect of varying combinations of several substrates and co-factors on the glycolysis and respiration of these cells has been studied also.[560] In typical chronic myelocytic leukemia and in polycythemia vera associated with leucocyte abnormalities there are distinctive and highly consistent biochemical patterns in terms of blood histamine, unit leucocyte alkaline phosphatase activity, and unit myeloid leucocyte glycogen.[561]

Chemistry: There is high histamine and low alkaline phosphatase and glycogen content in cells from chronic myelocytic leukemia,[43e] in contrast to a high content of all three found in polycythemia vera. Other myeloproliferative disorders show no constant relation.

The β-glucuronidase activity of separated leucocytes from normal subjects and from subjects with various types of leukemia and other diseases has been studied, but the results do not permit a functional interpretation.[562]

The nucleotidase of leucocytes has been identified as an acid phosphatase with a pH optimum of 4.0. Nucleotidase activity measures 10 times greater in the granulocyte than in the lymphocyte.[510] Leukemia is sometimes accompanied by severe hypokalemia [563]; hyperkalemia may occur during extensive destruction of leukemic tissue.

The Immune Response: Significantly lower titers of immune hemolysins for sheep and chicken erythrocytes are found in mice after development of leukemia.[564] The depressing effect on antibodies is limited to hemolysins. The ability to form antibody to pneumococcus capsular polysaccharides is influenced by the type of leukemia present.[565] There is a distinct impairment of antibody response in acute leukemia upon cortisone administration.

Etiology and Classification.—The incidence of leukemia in the exposed survivors of Hiroshima and Nagasaki shows a significant increase as compared with the non-exposed population of two other cities. These findings support the concept that irradiation from the atomic bomb explosions may be leukemogenic in man. An increased incidence of leukemia (1.2%) has been found among all physicians by analyzing the causes of deaths as stated in the necrologies appearing in *The Journal of the American Medical Association* from 1947 to 1951.[41a] The increased incidence

559. Beck, W. S., and Valentine, W. N.: The Aerobic Carbohydrate Metabolism of Leukocytes in Health and Leukemia: I. Glycosis and Respiration, Cancer Res. **12**:818, 1952.

560. Beck, W. S., and Valentine, W. N.: The Aerobic Carbohydrate Metabolism of Leukocytes in Health and Leukemia: II. The Effect of Various Substrates and Coenzymes on Glycolysis and Respiration, Cancer Res. **12**:823, 1952.

561. Valentine, W. N.; Beck, W. S.; Follette, J. H.; Mills, H., and Lawrence, J. S.: Biochemical Studies in Chronic Myelocytic Leukemia, Polycythemia Vera and Other Idiopathic Myeloproliferative Disorders, Blood **7**:959, 1952.

562. Follette, J. H.; Valentine, W. N., and Lawrence, J. S.: The Beta Glucuronidase Content of Human Leukocytes in Health and in Disease, J. Lab. & Clin. Med. **40**:825, 1952.

563. Videback, A.: Continued Studies of Plasma-Potassium Levels in Leukemia, Acta med. scandinav. **144**:160, 1952.

564. Davidsohn, I., and Stern, K.: Hemoantibodies in Mouse Leukemia, Cancer Res. **12**:256, 1952.

565. Larson, D. L.: Quantitative Antibody Studies in Man: Antibody Response in Leukemia and Allied Disorders, abstracted, J. Clin. Invest. **31**:645, 1952.

had been shown previously in radiologists. The more widespread use of the fluoroscope has been incriminated.

Data on the inheritance of human leukemia are meager. In one family leukemia was absent for three generations before appearing in a fourth generation daughter (myelogenous type).[125b] This woman mated with a nonleukemic man, produced four normal children. A nonleukemic brother had one child with acute lymphatic leukemia and a cousin had one child with myelogenous leukemia. In another family, three brothers had chronic lymphatic leukemia.[125e] In one of these the disease began at the unusual age of 22 years.

Arguments in favor of eosinophilic leukemia being a distinct type have again been reported.[566] A similar argument is advanced also for monocytic leukemia.[567]

At the University of Illinois, an analysis of 916 cases of leukemia in patients ranging in age from infancy to 82 years has revealed a sharp peak between 2 and 6 years of age, due primarily to acute types. Incidence is low in adolescence but shows a gradual rise to a second peak at 55 years, mainly of the chronic leukemias.[125a] The incidence of leukemia in new white clinic patients is 0.26%, as compared with 0.04% in Negro patients; leukemic types are approximately the same in both. Myeloblastic leukemia has been reported in an 8-day-old infant.[125d] The oldest known patient with leukemia is a 102-year-old woman.[87c]

Symptoms, Complications, and Course in Leukemia.—The symptoms in leukemia are generally referable to (1) a local accumulation of cells that cause symptoms by mechanical means per se, i. e., marked splenomegaly, cervical adenopathy, and (2) symptoms that are referable to a diminution of formed elements of the blood caused by the myelophthisic replacement of the normal cell elements with the leukemic cell. The various syndromes associated with granulocytopenia, anemia, and/or thrombocytopenia would be manifested in the second group.

Unusual manifestations in leukemia may occasionally make the diagnosis difficult. The initial symptoms in a case of acute myelogenous leukemia simulated those of acute appendicitis.[568] Skin lesions in a case of acute myeloblastic leukemia in an 8-day-old infant simulated those seen in urticaria pigmentosa.[125d] Bullous eruptions on the palms and soles and other various skin lesions have been noted, particularly in the chronic types.[569] Uterine hemorrhage may also be an early manifestation of leukemia.[570]

The advent of therapy with antibiotics and transfusions has diminished significantly the complications due to infection and hemorrhage, thus allowing other complications, such as leukemic pericarditis, to be recognized.[571] Leukemia as a complication in pregnancy is rare. In one instance spontaneous premature delivery resulted in survival of the normal infant and death of the leukemic mother.[125c]

566. Hyman, H. L., and Jarrold, T.: Eosinophilic Leukemia: Report of a Case with Autopsy, Ann. Int. Med. **36**:1541, 1952.

567. Jimenez-Diaz, C.; Morales, M., and Paniagua, G.: Leucémie monocytaire, Acta haemat. **8**:131, 1952.

568. Charest, L. R., and Holt, C. L.: Acute Myelogenous Leukemia Simulating Acute Appendicitis, J. Internat. Coll. Surgeons **17**:445, 1952.

569. Scutt, R.: Bullous Lesions in Leukemia, Brit. M. J. **1**:139, 1952.

570. Wheaton, C. E. W.: Leukemia with Primary Gynecological Manifestations, Brit. M. J. **1**:30, 1952.

571. Bierman, H. R.; Perkins, E. K., and Ortega, P.: Pericarditis in Patients with Leukemia, Am. Heart J. **43**:413, 1952.

Women with acute leukemia, particularly of the monocytic type, frequently manifest improvement on becoming pregnant. Exacerbation is frequent soon after delivery.[549]

It was mentioned previously (page 401) that hemolytic anemia is frequently associated with chronic leukemia. Berlin[572] and Ross and his associates[573] and others have called attention to the significance of the hemolytic component of the anemias of malignancy. Many of these entities are so-called "secondary hypersplenism," and removal of the spleen may result in a reestablishment of the erythroid equilibrium. The new steroids also may assist in curbing increased red cell destruction. At times, however, the hemolytic process fails to respond to either type of therapy. Erythrocytes from a large group of leukemic patients exhibited an increased osmotic fragility.[422b]

Rodgers and his associates have reviewed the histories of 148 children with leukemia prior to treatment with the folic acid antagonists.[574] Over 90% of the patients of this series had acute fulminating leukemia, with an average duration of life of less than three months. No chronic granulocytic leukemia was encountered in this series.

Survival of 17 years in an elderly patient with chronic myelogenous leukemia has been observed.[575] A case of lymphatic leukemia which converted to Hodgkin's disease has been described.[576]

Further discussion of the course in leukemias is continued in the therapy section (page 429).

Multiple Myeloma.—Multiple myeloma has been reviewed in several reports.[577] In the order of frequency, the most common laboratory findings are excessively high erythrocyte sedimentation rates, anemia, hyperproteinemia, the presence of myeloma cells in the peripheral blood, Bence-Jones proteinuria, excessive rouleaux formation, hypercalcemia, and extramedullary lesions.[578] Cold-precipitable globulins (cryoglobulins) are present in the serum in a high proportion of cases.[556]

Multiple myeloma and plasmacytic leukemia have been considered to be only different clinical expressions of the same disease.[579] Despite common characteristics, differential points have been pointed out.[580]

572. Berlin, R.: Red Cell Survival Studies in Normal and Leukaemic Subjects, Acta med. scandinav. **139**:9, 1951.

573. Ross, J. F.; Crockett, C. L., Jr.; Finch, S. C., and Emerson, C. P.: The Mechanism of Anemia in Leukemia and Malignant Lymphoma; abstracted, J. Clin. Invest. **30**:668, 1951; read before Second National Cancer Conference, Cincinnati, March 3-5, 1952.

574. Rodgers, C. L.; Donohue, W. L., and Snelling, C. E.: Leukaemia in Children, Canad. M. A. J. **65**:548, 1951.

575. van der Werff, J. T.: A Case of Extremely Long Survival in Chronic Myelogenous Leukemia, Brit. J. Radiol. **25**:52, 1952.

576. Krim, M.; Meyer, L. M.; Rosenthal, J., and Ritz, N. D.: Conversion of Lymphocytic Leukemia to Hodgkin's Disease, A. M. A. Arch. Int. Med. **89**:297, 1952.

577. Powell, W. N.: Clinical Pathology of Multiple Myeloma, Texas J. Med. **48**:18, 1952. Gailitis, J., and Caputi, A.: Multiple Myeloma, Rhode Island M. J. **35**:308, 1952.

578. Hayes, D. W.; Bennett, W. A., and Heck, F. J.: Extramedullary Lesions in Multiple Myeloma, A. M. A. Arch. Path. **53**:262, 1952.

579. Goldman, R.; Adams, W. S., and Luchsinger, E. B.: Renal Function in Multiple Myeloma, J. Lab. & Clin. Med. **40**:519, 1952.

580. Majeranowski, J. F.: Subleukemic Plasma Cell Leukemia, A. M. A. Arch. Path. **53**:593, 1952.

Glomerular filtration rate, renal plasma flow, and tubular excretory mass were determined in 9 patients with multiple myeloma and in 10 normal persons.[579] The mean values were significantly lower in patients with multiple myeloma. Further study suggested that destruction was of entire nephron units.

A sensitive adjunct in the diagnosis of multiple myeloma has resulted from the use of immune rabbit serum specific for chemically proved Bence-Jones protein.[28]

Hodgkin's Syndrome.—"The pendulum of opinion is swinging again in favor of an infectious cause of Hodgkin's disease, and an increasing mass of experimental data has demonstrated that virus-type factors are intimately associated with the Hodgkin's granuloma" (Bostick [541]).

In electron microscope studies on macromolecular particles from human neoplastic and nonneoplastic lymph nodes, the majority of the particles are in the 10 to 20 mμ range in the Hodgkin disease group and in other lymphomas. In the carcinomas the greatest number are in the 20 to 30 mμ size range. The nonneoplastic preparations as a group have no predominant size range.[581] Cytochemical evidence suggests the reticulum cell origin of the Reed-Sternberg cell.[582] In vitro cultures of lymph nodes from patients having Hodgkin's disease [583] show that elongated reticulum cells and reticular clasmatocytes occur in greater numbers than in cultures from nodes having a less marked reticulum cell hyperplasia.

Attempts to use adenine nucleotide blood-level determinations diagnostically in Hodgkin's disease are unsuccessful.[584] The immunologic response is unimpaired except in the final stages.[585] The prognosis is better in the paragranuloma type than in the sarcoma type.[586] An interpretation of true conversion of a case of lymphocytic leukemia to Hodgkin's disease was based on the lack of evidence of leukemia terminally.[576]

Pregnancy produces no exacerbation in the disease, which has, in turn, no effect on ovulation, fertility, incidence of abortion, or antepartum and postpartum hemorrhages.[127b] Hodgkin's syndrome may be complicated by low platelet count with resulting purpura,[587] cardiac envolvement,[587] pulmonary cavications,[588] and infraclavicular chest wall tumors.[589]

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581. Hoster, M. S.; Van Winkle, Q.; Rabatin, J. G., and Hoster, H. A.: Macromolecular Particles Obtained from Human Neoplastic and Non-Neoplastic Lymph Nodes: II. Electron Microscope Study, Cancer Res. **12**:69, 1952.

582. Ackerman, G. A.; Knouff, R. A., and Hoster, H. A.: Cytochemistry and Morphology of Neoplastic and Nonneoplastic Human Lymph Node Cells with Special Reference to Hodgkin's Disease, J. Nat. Cancer Inst. **12**:465, 1951.

583. Ackerman, G. A.; Knouff, R. A., and Hoster, H. A.: Cytochemistry and Morphology of Human Lymph Node Cells Grown in Vitro, J. Nat. Cancer Inst. **12**:1267, 1952.

584. Rottino, A.; Hoffman, G. T., and Albaum, H.: Adenine Nucleotide Content of Red Blood Cells of Normal Individuals and of Patients Suffering from Hodgkin's Disease and Other Diseases, Blood **7**:836, 1952.

585. Hoffman, G. T., and Rottino, A.: Studies of Immunologic Reactions of Patients with Hodgkin's Disease, Quart. Rev. Allergy **6**:48, 1952.

586. Harrison, C. V.: Benign Hodgkin's Disease (Hodgkin's Paragranuloma), J. Path. & Bact. **64**:513, 1952.

587. Rottina, A., and Hoffman, G. T.: Cardiac Involvement in Hodgkin's Disease, Am. Heart J. **43**:115, 1952.

588. Dickson, R. J., and Smitham, J. H.: Cavitation of Lung Lesions in Hodgkin's Disease: A Report of 2 Cases, Brit. J. Radiol. **25**:48, 1952.

589. Goldman, R.: Infraclavicular Chest Wall Tumors in Hodgkin's Disease, California Med. **76**:38, 1952.

Treatment of Leukemias and Lymphomas.—The 1952 literature on leukemia and lymphoma is broad, voluminous, and repetitious. The great variation of opinion, too often based on subjective rather than objective findings, has added to the problem of summarizing the pertinent information into a utilizable form. There are some excellent objective studies; however, even in these the evaluation is limited by the lack of satisfactory criteria for evaluation. In order to facilitate conveyance of the pertinent information in the reviewed literature, we have attempted to express the consensus of opinion regarding the treatment of the leukemias and lymphomas. To this we have incorporated some items from our own experiences. The major portion of this section deals with therapeutic measures investigated; a final listing includes the preferred therapy in each specific disease. Our review has included the articles listed in the footnotes.[590]

590. (*a*) Rohn, R. J., and Bond, W. H.: The Effects of Nitrogen Mustards and Triethylene Melamine in Disseminated Lupus Erythematosus, abstracted, J. Lab. & Clin. Med. **40**:934, 1952. (*b*) Meyer, L. M.; Schwartz, S. O.; Sawitsky, A.; Beyers, M. R.; Ritz, N. D.; Brahin, C.; Diefenbach, W.; Kleinschmidt, W., and Friedmann, I.: Treatment of Lymphomatous Diseases with Triethylene Melamine, Acta med. scandinav., Supp. *272*, p. 3, 1952. (*c*) Holt, C. L., and Porter, J. E.: The Treatment of Neoplasms with Nitrogen Mustards, J. Maine M. A. **43**:86, 1952. (*d*) Wright, J. C.; Prigot, A.; Wright, L. T., and Arone, I.: Further Observations of the Use of Triethylene Melamine in Neoplastic Diseases, A. M. A. Arch. Int. Med. **89**:387, 1952. (*e*) Kravits, S. C.; Diamond, H. D., and Craver, L. F.: The Clinical Use of Triethylene Melamine, Blood **7**:729, 1952. (*f*) Rundles, R. W., and Barton, W. B.: Triethylene Melamine in the Treatment of Neoplastic Disease, ibid. **7**:483, 1952. (*g*) Bayrd, E. D.; Stickney, J. M.; Hall, B. E., and Watkins, C. H.: Clinical Observations on the Use of Triethylenemelamine, Cancer **5**:336, 1952. (*h*) Silverberg, J. H., and Dameshek, W.: Use of Triethylene Melamine in Treatment of Leukemia and Leukosarcoma, J. A. M. A. **148**:1015, 1952. (*i*) Osgood, E. E., and Seaman, A. J.: Treatment of Chronic Leukemias: Results of Therapy by Titrated, Regularly Spaced Total Body Radioactive Phosphorus, or Roentgen Irradiation, ibid. **150**:1372, 1952. (*j*) Weir, D. R.: Effect of Desoxypyridoxine on Acute Lymphatic Leukemia of Adults, abstracted, J. Clin. Invest. **31**:670, 1952. (*k*) Sykes, M. P.: Treatment of the Leukemias and Lymphomas: Current Trends, J. Am. M. Women's A. **7**:321, 1952. (*l*) Friedman, I. A.: The Use of Judgment in the Treatment of Leukemia, Chicago M. School Quart. **13**:126, 1952. (*m*) Frumin, A. M.; Pfeiffer, M. C. J.; Cameron, M. H.; Calesnick, B., and Smith, E.: Hematologic Therapy: Some Recent Advances, J. Am. M. Women's A. **7**:197, 1952. (*n*) Sturgis, C. C.: Some Aspects of the Leukemia Problem, J. A. M. A. **150**:1551, 1952. (*o*) Proceedings of the Second Conference on Folic Acid Antagonists in the Treatment of Leukemia, Blood (Supp.) **7**:1, 1952. (*p*) Klingberg, W. G.: Therapy of Acute Leukemia in Children, J. Arkansas M. Soc. **48**:227, 1952. (*q*) Poncher, H. G.; Waisman, H. A.; Richmond, J. B.; Horak, O. A., and Limarzi, L. R.: Treatment of Acute Leukemia in Children With and Without Folic Acid Antagonists, J. Pediat. **41**:377, 1952. (*r*) Dresner, E., and White, J. C.: The Biological Action and Clinical Application of Folic Acid Antagonists, Acta haemat. **7**:117, 1952. (*s*) Sawitsky, A.; Ritz, N. D.; Jacobson, J.; Meyer, L. M.; Schwartz, S. O.; Krim, M.; Bock, G., and Brahin, C. M.: Treatment of Acute Leukemia with Anti-Folic Acid Compounds (Aminopterin and Aminoanfol), Cancer **5**:344, 1952. (*t*) Cottle, R. I., and Battle, J. D., Jr.: Treatment of Acute Lymphatic Leukemia with Aminopterin, Cleveland Clin. Quart. **19**:67, 1952. (*u*) Bruton, O. C., and Price, W. S.: Treatment of Leukemia in Children, U. S. Armed Forces M. J. **3**:461, 1952. (*v*) Swendseid, M. E.; Swanson, A. L.; Miller, S., and Bethell, F. H.: The Metabolic Displacement of Folic Acid by Aminopterin. Studies in Leukemia Patients, Blood **7**:302, 1952. (*w*) Swenseid, M. E.; Swanson, A. L.; Meyers, M. C., and Bethell, F. H.: The Nutritional Status of Folic Acid in Persons with Leukemia and Its Possible Relation to Effects of Aminopterin Therapy, ibid. **7**:307, 1952. (*x*) Gendel, B. R.; Kraus, A. P., and Green, F. D.: Aminopterin in the Treatment of Acute Leukemia of Adults, Am. Pract. & Digest. Treat. **3**:97, 1952. (*y*) Leikin, S.;

(Footnote continued on next page)

Therapeutics: The therapeutic measures investigated are divided into three categories: (1) chemotherapeutic agents, (2) irradiation, and (3) surgery.

Chemotherapeutic agents. The problem of finding effective agents for treatment of leukemia and lymphoma

is almost—not quite, but almost—as hard as finding some agent that will dissolve away the left ear, say, yet leave the right ear unharmed; so slight is the difference between the cancer cell and its normal ancestor (Woglom, quoted by Sykes[590k]).

1. Methyl-*bis* (β-chloroethyl) amine hydrochloride (nitrogen mustard). Nitrogen mustard is most valuable in those lymphomas which are of a generalized character. In mediastinal and spinal lesions postirradiation edema of the nodes may add pressure complications. Nitrogen mustard is preferable to roentgen radiation in these situations, but it should be followed by irradiation therapy for a prolonged remission.

Disadvantages of nitrogen mustard are that (1) it requires intravenous administration, which may be complicated by venous thrombosis; (2) it produces severe nausea and vomiting for several days in 80 to 85% of the cases; (3) there is a relatively narrow margin of safety,[590c] for instance, posttherapeutic graulocytopenia and thrombocytopenia may be the bases for additional symptoms; (4) large masses rarely respond adequately, and the remissions produced are relatively brief.

The most effective therapy with nitrogen mustard is in the Hodgkin syndrome.[590k,l] In many instances, when the lesions apparently became radio-resistant, a course of nitrogen mustard will assist in reestablishing radio-sensitivity. Results of cautious combined use of nitrogen mustard and intense roentgen radiation are encouraging. Other diseases treated with nitrogen mustard with varying degrees of success are acute monocytic leukemia, chronic myelogenous leukemia, mycosis fungoides, follicular lymphoblastoma, reticulum cell sarcoma, and polycythemia vera.

Rice, E. C.; Bell, D. F., Jr., and Waters, R. J.: The Treatment of Acute Leukemia in Children, J. Pediat. **41**:40, 1952. (*z*) Stout, A. P.: Surgical Treatment of Lymphosarcoma, Read Before Second National Cancer Conference, Cincinnati, March 3-5, 1952. (*a'*) Rundles, R. W.: Chemotherapy: Urethane (Lymphoma and Leukemia), Read Before Second National Cancer Conference, Cincinnati, March 3-5, 1952. (*b'*) Karnofsky, D.: Chemotherapy: Mustards (Lymphoma and Leukemia), Read Before Second National Cancer Conference, Cincinnati, March 3-5, 1952. (*c'*) Farber, S.: Therapy: General Summation (Lymphoma and Leukemia), Read Before Second National Cancer Conference, Cincinnati, March 3-5, 1952. (*d'*) Eliel, L. P., and Pearson, O. H.: Chemotherapy: Hormones (Lymphoma and Leukemia), Read Before Second National Cancer Conference, Cincinnati, March 3-5, 1952. (*e'*) Weisberger, A. S.; Heinle, R. W., and Levine, B.: Some Structural Requirements for the Prevention of Leukopenia Induced by Nitrogen Mustard, J. Clin. Invest. **31**:217, 1952. (*f'*) Alpert, L. K.: Triethylene Melamine in Malignant Disease; abstracted, ibid. **31**:614, 1952. (*g'*) Luttgens, W. F., and Bayrd, E. D.: Treatment of Multiple Myeloma with Urethane, J. A. M. A. **147**:824, 1951. (*h'*) Alwall, N.: Urethane in Multiple Myeloma: I. Final Report of a Case Treated More Than 4 Years with Urethane, Acta med. scandinav. **144**:114, 1952. (*i'*) Meacham, G. C.; Tillotson, F. W., and Heinle, R. W.: Liver Damage After Prolonged Urethane Therapy, Am. J. Clin. Path. **22**:22, 1952. (*j'*) Burchenal, J. H.; Karnofsky, D. A.; Murphy, L.; Ellison, R. R., and Rhoads, C. P.: Effects of 6-Mercaptopurine in Man, Proc. Am. A. Cancer Res. **1**:7, 1953. (*k'*) Farber, S.; Foley, G.; Downing, V.; Appleton, R., and King, J.: Antimetabolite, Antimalarial, and Anticancer Activity of a Series of New Dihydrotriazines, ibid. **1**:15, 1953. (*l'*) Duffy, B. J., Jr., and Howland, J. W.: Radiophosphorus (P^{32}) in Diagnosis and Treatment, New York J. Med. **52**:551, 1952. (*m'*) Wiseman, B. K.; Albala, M., and Schafer, R. L.: Personal communication to the authors. (*n'*) Morris, W. R.: Gastric Hodgkin's Disease J. A. M. A. **149**:1460, 1952.

In experimental animals the severe leukopenia induced by nitrogen mustard [590e] is alleviated by l-cysteine hydrochloride.

2. Triethylene melamine (2,4,6,-triethyleneimino-*s*-triazine). Triethylene melamine, a compound closely related to nitrogen mustard, was first synthesized in Germany and was used in the textile industry for the improvement of the finish of rayon fabrics.[590k]

It has subsequently been found to have nitrogen-mustard-like effects on experimental tumors and leukemia in mice. The action of triethylene melamine on normal and neoplastic tissues is apparently the same as that of nitrogen mustard.[590m] Its activity is attributed to the ethyleneimine ring, which is similar to the active hydrolyzate of nitrogen mustard.[590h] By weight it is two to three times as active.

Advantages of triethylene melamine are that (1) it may be given orally, thus avoiding the danger of venous thrombosis [590h]; (2) the number of hospital admissions is reduced; (3) the marked nausea and vomiting associated with nitrogen mustard is less severe.[590k,m] Anorexia is frequently the only symptom. Disadvantages are that the action is slower,[590h] averaging nine days for relief of symptoms compared to two to five days with nitrogen mustard, and, similarly, marrow depression and recovery are slower and more difficult to evaluate. This accounts for the lower margin of safety as compared with nitrogen mustard. The individual variability of tolerance is wide.[590e,f] Irreversible marrow hypoplasias have been reported. Renal damage may be sufficiently severe to cause death.[590g]

As with nitrogen mustard, cautious combined use of roentgen radiation therapy may be beneficial.[590e,f] Triethylene melamine is most effective in Hodgkin's syndrome [591] and reticulum cell sarcoma and less effective in the leukemias,[590b] polycythemia vera, and lupus erythematosus. In situations where radioactive phosphorus is not available triethylene melamine is an adequate substitute in the treatment of polycythemia vera and chronic leukemias. As a chronic marrow depressant, it is preferred in these diseases to intravenous nitrogen mustard.

3. Folic acid antagonist. The isolation, identification, and final synthesis (1945) of the folic acid molecule was another milestone in medicine. This essential molecule for many animal organisms was the entree to production of many related molecules, several of which are physiologically antagonistic to the parent molecule. Farber's use of the folic acid antagonists in 1948 initiated a great impetus in the chemotherapy of leukemia.

The antagonists most frequently used have been aminopterin (4-aminopteroylglutamic acid), amethopterin (4-amino-N-10-methylpteroyl glutamic acid), amino-an-fol (4-aminopteroylaspartic acid), adenopterin (4-amino-9k-10-dimethylpteroylglutamic acid), and aminoteropterin (4-aminopteroyltriglutamic acid).

A careful evaluation of available statistics indicates that life is prolonged by the use of antagonists, although there are some opinions to the contrary.[590d] Most persons having broad experience with the use of these drugs admit not only a prolongation of actual life, but a prolongation of useful life, which is even more important.[590m,q] Reported series vary. A possible basis for this is that some investigators differentiate the cellular types of acute leukemia, while others consider them all as a single group. Effective remissions have been produced in approximately

591. Footnote 590*d*, *g*, *h*, and *k*.

60% of the cases of acute lymphocytic leukemia. Repeated remissions may occur; however, the effectiveness of the antagonists generally decreases in successive relapses. Children respond much better than adults.

The antagonists may be administered parenterally or, preferably, orally. There is disagreement on intermittent or continuous therapy. Several reports assert that clinically some patients may get worse before they get better, and this is presented as an argument for continuous therapy. When therapy is continuous, frequent and careful hematologic studies are mandatory. Approximately 2 to 15 weeks may elapse before occurrence of remission. In the most satisfactory remissions there is a complete return of the peripheral blood picture to normal. This is a reflection of an almost normal marrow production. However, a complete disappearance of the malignant cells from the marrow rarely occurs.

The most common toxic effect is stomatitis. This is alleviated by diminishing or discontinuing the drug temporarily. The citrovorum factor (folinic acid or Leukovorin) is claimed to be of benefit; however, there is not agreement on this.[590m] Marked ulcerations with secondary hemorrhage have also been seen in the intestine at postmortem examination of patients receiving antifolic therapy.

The problem of toxicity has been minimized in great part by experience. As Farber states,

> If the problem of resistance, either initial or acquired, of the leukemic cell to the folic acid antagonist could be solved, the usefulness of the antagonists in acute leukemia could be compared with justice to that of insulin in diabetes.[590c']

Although the precise mode of action of the folic acid antagonists is as yet undefined, available evidence has enabled Poncher and his associates [590q] to propose that aminopterin acts as a metabolic antagonist in the formation both of folic acid and of the citrovorum factor (Fig. 1).

The predilection of these antagonists for leukemic cells has been explained on a rate differential basis. For instance, leukemic cells are geared to more active biosynthesis. Thus they may reflect more readily any inhibition of the factors involved in nucleoprotein synthesis.

The development of resistance to the antifolic drugs is attributed to spontaneous mutation of some cell of the nonresistant population to a resistant form. The therapeutic agent is thus favorably selective for the resistant cells,[590o] so much so that instances are cited of resistant cells becoming dependent on the antagonist for optimal proliferation. This theory does not satisfactorily explain the frequent occurrence of refractiveness to antifolic therapy in virgin cases. Cells resistant to the anti-folic-acid agents can be inhibited by other antileukemic agents, such as triethylene melamine.

4. Corticotropin and cortisone. There is a scattering of reports on the use of corticotropin and cortisone alone as treatment for the acute leukemias. The trend recently is to utilize cortisone or corticotropin as part of the initial therapy when the patient is critically ill and then to shift to the anti-folic-acid agents.[590k] Judicious combined use has given the longest survival in some critically controlled groups. Tissue atrophy associated with steroid therapy has been combatted by testosterone.[590d']

The steroids have varying results in the treatment of lymphosarcoma, chronic leukemias, and multiple myeloma.

5. Ethyl-carbamate (urethane): Urethane has proved a valuable adjunct in treating chronic myeloid leukemia[590k] and multiple myeloma.[590g',h'] The enteric-coated tablets have minimized gastrointestinal irritation. This oral therapy may be used as "maintenance" therapy. This requires weekly total white cell counts, and dosage is regulated by the trend of the count rather than by a single isolated count. The maximum response of a heavy dosage at any particular moment is reflected in the peripheral blood 10 to 13 days later. Therefore, the daily amount is adjusted to the rising or falling trend of the count. For a margin of safety the total white count is not allowed to go below 10,000 per cubic centimeter in the leukemias.

Urethane is a comparatively safe chemical to use clinically, but it occasionally produces a hemorrhagic and degenerative centrilobular hepatic lesion which may be irreversible.[590o,a'] At the present time, this does not contraindicate the use of prolonged urethane therapy. However, it is quite possible that the picture may change.

6. Other therapeutic agents. Regression of the lymphadenopathy and splenomegaly in three patients with acute lymphocytic leukemia was accomplished with deoxypyridoxine.[590j] It requires further evaluation. Among the many other chemicals under study in the treatment of the lymphomas and leukemias are SK 3818 (also known as TEPA, an ethylenimine derivative of phosphoric acid with nitrogen-mustard-like qualities), G.T. 41 (1,4-dimethyl sulfonyl butane), isoniazid (isonicotinic acid, Nydrazid, Ditubin),[590k] 6-mercaptopurine (Purinethol),[590j'] and a series of dihydrotriazines.[590k'] The use of various injectable viruses as therapeutic agents for the destruction of neoplastic tissue is in the investigative state.[590k]

Irradiation. Roentgen radiation is still the therapeutic standby for the lymphomas and chronic leukemias.[590k] In an excellent review of their program of treatment of chronic leukemias with spray roentgen radiation or radioactive phosphorus Osgood and Seaman[590l] have presented evidence for a statistically significant prolongation of life of patients so treated. Eight-five per cent of the postherapy time of patients was spent at their usual occupations and recreations. The need for transfusions was markedly reduced. The lymphomas were best treated by localized irradiation.

Radioactive phosphorus (P^{32}) is an excellent means of internal irradiation. It emits only beta irradiation and has a half-life of only 14.3 days. The predilection for deposition is in the cortex of bone and in the nuclei of rapidly multiplying cells. The short penetrating beta rays may thus directly irradiate the narrow extracellularly; also, there is intracellular irradiation from the nuclei of rapidly formed neoplastic cells. The supply of P^{32} is relatively plentiful. It is obtainable through the Atomic Energy Commission by certain institutions able to fulfill the monitoring regulations, etc. It is also now available commercially (Abbott Laboratories). The requirements, though still under Atomic Energy Commission supervision, are less rigid for material from the latter source. If the oral route is used the P^{32} should be given in a fasting state and afterwards food should also be withheld for two hours.

Radioactive phosphorus is effective in treating polycythemia vera,[592] chronic myelogenous leukemia, chronic lymphocytic leukemia[590k,l'] and the Cohnheim type of lymphocytic leukemia.

592. Abbatt, J. D.: Recent Advances in the Treatment of Polycythaemia Vera, Practitioner **168**:243 (March) 1952.

The situation of the so called "packed" bone marrow in chronic lymphocytic leukemia is frequently quite challenging. It occurs when there is a history of a progressive downhill course clinically and hematologically (i. e., anemia and thrombocytopenia) in the face of heavy irradiation therapy, either with x-ray to spleen and lymph nodes or with radioactive phosphorus. On attempting aspiration of the marrow, which is necessary for differentiating it from a hypoplastic or aplastic condition, one is unable to obtain marrow or even blood with maximum negative pressure from several sites. This is significant of a profound hyperplasia with lymphocytic leukemia cells, resulting in a relative avascularity and "packed" marrow. Wiseman [590m'] has used a method of roentgen irradiation therapy to "flat" bones which has been quite successful. Two ports daily of 75 to 150 r are given; i. e., one each 40 by 40 cm. port over the anterior and the posterior thorax on one day, and one each 20 by 40 cm. port over the anterior and the posterior pelvis on the following day. A 250 kv. machine is used at 1 meter focus-skin distance with Thoraeus 3 filter and half value layer of 3.0 mm. copper. Additional courses are given if adequate results are not obtained within several weeks after the first series. The "log jam" effect is thus frequently relieved, and space for erythroid and platelet proliferation is created. An elevated reticulocyte count followed by an elevation of the red cell count, hemoglobin, and platelet count is reflected in the clinical improvement. The danger of hypoplasia or aplasia is minimal if care is used.

Surgery. Resection is recommended in early and circumscribed cases of the Hodgkin syndrome and in those lymphosarcomas that show evidence of the biological type of tumor of focal origin which naturally pursues a slow course.[590k, n'] Supplementation with intense roentgen irradiation is advised.

Splenectomy [593] in hemolytic anemias complicating chronic leukemia has been discussed on page 410.

Summarization of Therapy in the Leukemias and Lymphomas: The only "cure" for leukemia is a change in the diagnosis. Many agents may temporarily reverse the progressive downhill course. It must be emphasized that a specific therapy is as efficient as the individual administering it. Excellent materials may be poorly used; secondary materials may be effectively used. Thus an evaluation cannot be dogmatic and must contain some element of subjectivity. The following summarization is on this basis.

Acute leukemia. Folic acid antagonists effect complete or partial improvement in about 60% of the cases of the lymphocytic type in children. Corticotropin and cortisone are adjuvants alone or in combination, in all types. Nitrogen mustard and triethylene melamine may produce temporary improvements, particularly in the monocytic type.

Chronic myelogenous leukemia. Localized roentgen irradiation, internal total body irradiation with radioactive phosphorus (P^{32}), and urethane are the most effective of the currently used agents. Nitrogen mustard, triethylene melamine, and total body roentgen irradiation are varyingly beneficial. The further evaluation of the use of G.T. 41 is being made. Corticotropin is occasionally helpful.

Chronic lymphocytic leukemia. The picture is the same as for chronic myelogenous leukemia, with the exception of urethane therapy. Therapy directed toward "loosening" the "packed marrow" has been previously outlined.

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593. Fisher, Welch, and Dameshek.[422e] Sturgis.[590n]

Hodgkin's disease. When the process is first manifested in a localized surgically accessible site, excision followed by intense irradiation is frequently effective. The trend has been toward intense irradiation at the area of first appearance. Nitrogen mustard and triethylene melamine are excellent accessory agents and occasionally may resensitize a radioresistant process.

Multiple myeloma. Urethane and localized roentgen irradiation are the standbys. Corticotropin and cortisone may rarely be beneficial adjuncts. Nitrogen mustard and triethylene melamine are relatively ineffective.

Lymphosarcoma and reticuloendotheliosis. The choice is between roentgen irradiation and nitrogen mustard. If the disease is manifested in localized tumors, surgical excision and irradiation are suggested. Remissions have been found to occur with corticotropin, folic acid antagonists, and triethylene melamine.

Follicular lymphoblastoma, reticulum cell sarcoma, and mycosis fungoides. These respond with varying success with roentgen irradiation, nitrogen mustard, and triethylene melamine.

Polycythemia vera. Radioactive phosphorus (P^{32}) judiciously used with venesections is extremely effective. Careful use of triethylene melamine, nitrogen mustard, and spray irradiation by several groups has been satisfactory.

PLATELETS

The resurgence of interest in platelets has been due to the refinement of new techniques and availability of new materials for more efficient recovery of functionally intact platelets. Among these are ion-exchange resins; new anticoagulants, i. e. ethylene diamine tetra-acetic acid (Sequestrene); various wetting agents, and refined differential centrifugation techniques.

In a study of 722 normal persons the platelet count was found to be considerably higher in younger women than in men,[594] whereas in older age groups there is no difference. In elderly persons no consistent change has been seen in total number of platelets or other formed elements.[595]

Chemical and Physical Studies of Platelets.—A cholinesterase of the same type as is found in erythrocytes has been noted in platelets of the rat,[596] cat, rabbit, dog, and horse.[597] The electrophoretic mobility of human platelets exposed to prothrombin conversion in recalcified defibrinated normal plasma remains normal.[598] Normal values have been obtained also in the majority of hematologic diseases

594. Josephson, B., and Dahlberg, G.: Variations in the Cell-Content and Chemical Composition of the Human Blood Due to Age, Sex and Season, Scandinav. J. Clin. & Lab. Invest. **6**:216, 1952.

595. Shapleigh, J. B.; Mayes, S., and Moore, C. V.: Hematologic Values in the Aged, in Cowdry, E. V.: Problems of Aging: Biological and Medical Aspects, Ed. 3, Baltimore, Williams & Wilkins Company, 1952.

596. Zajicek, J., and Datta, N.: Acetylcholine Esterase in Thrombocytes of Rat Blood, Acta haemat. **7**:39, 1952.

597. Augustinsson, K. B.; Datta, N.; Grahn, M., and Zajicek, J.: Acetylcholinesterase in Thrombocytes, Nature, London, **169**:800, 1952.

598. Bigelow, F. S., and Desforges, J. F.: Mobility of Human Platelets in a Microelectrophoresis Cell, Proceedings American Federation Clinical Research, National Meeting, Atlantic City, N. J., May 4, 1952.

studied, the exceptions occurring in platelets from two patients with acute thrombocytopenia associated with tuberculosis and cirrhosis, respectively.[598] The relation of surface charge to platelet agglutination has yet to be demonstrated.

Although washed platelets exhibit oxygen consumption and glucose utilization on storage, they lose their ability to cause clot contraction in 24 hours, and oxygen consumption decreased to zero in three days. Their effect on clotting time and serum prothrombin time persists for several weeks.[599]

The enhanced thromboplastic activity of washed platelets exposed to thrombin suggests an additional accelerating influence on coagulation.[600] A directly proportional relation between the platelet-agglutinating property of serum and its prothrombin activity has been noted; failure to remove prothrombin from a serum being tested for platelet antibodies may result in false positive results.[601]

A platelet factor designated as "Factor 3" has been found to be a phosphatide which neutralizes heparin and possesses thromboplastic activity.[602] Clot retraction is proportional to the number of adhesive platelets and not to the total number of platelets.[603] A direct relation has been shown between fibrinogen concentration and the number of platelets necessary to promote any fixed level of clot contraction.[603] Further studies relate the physical behavior of platelets and thrombin formation and retraction.[604] The finding that platelets in persons with multiple sclerosis[605] are more adhesive than normal was considered as indicating a possible etiologic factor.

Thrombasthenia.—Thrombasthenia, a qualitative defect in platelets causing deficient clot retraction, has been reviewed.[606] Electron microscope studies show characteristic anomalies of the platelets.[606b]

A somewhat different clotting defect has been ascribed to platelet abnormalities in the activation of the thromboplastinogen to thromboplastin phase of coagulation.[607]

599. Hirsch, E. O.; Gardner, F. H., and Thomas, E. D.: Isolation and Concentration of Human Blood Platelets: Their Properties in Vitro and in Vivo, abstracted, J. Clin. Invest. **31**:638, 1952.

600. Desforges, J. F., and Bigelow, F. S.: The Acceleration of Clotting by Platelets Treated with Thrombin Preparations, J. Clin. Invest. **31**:625, 1952.

601. Stefanini, M., and Silverberg, J. H.: Studies on Platelets: I. The Relationship of Platelet Agglutination to the Mechanism of Blood Coagulation, Am. J. Clin. Path. **21**:1030, 1951.

602. Creveld, C., and Paulssen, M. M. P.: Isolation and Properties of the Third Clotting Factor in Blood-Platelets, Lancet **1**:23, 1952.

603. Still, B. M.: Experiments on Plasma Clot Contraction, Blood **7**:808, 1952.

604. Jürgens, R.: Die Blutplättchen und ihre Bedeutung für Blutungsneigung und Thrombusbildung, Deutsche med. Wchnschr. **77**:1265, 1952. Fonio, A.: Über die Wirkung des Hyalomers der Thrombocyten auf den Retraktionsvorgang, Acta haemat. **8**:363, 1952.

605. Nathanson, M., and Savitsky, J. P.: Platelet Adhesive Index Studies in Multiple Sclerosis and Other Neurologic Disorders, Bull. New York Acad. Med. **28**:462, 1952.

606. (*a*) Salomon, L., and Santiago, E. P.: Thrombocytoasthenias: Multiple Syndromes Due to Qualitative Platelet Deficiencies, Proceedings American Federation Clinical Research, National Meeting, Atlantic City, N. J., May 4, 1952. (*b*) Glanzmann, E.: Thrombopathien in der ersten Lebenszeit, Ann. pædiat. **178**:349, 1952.

607. Sussman, L. N.; Wald, N., and Rosenthal, R. L.: A Hemorrhagic Diathesis Due to a Qualitative Platelet Defect, Blood **7**:1100, 1952.

Thrombocytopenic Purpura.—The spectacular advances in this field in the last several years have resulted in a revision of many accepted concepts. There is no entirely satisfactory classification currently in use, due to much overlapping in basic abnormalities. Realizing this, however, for facilitating discussion we have grouped these entities into (1) peripheral (megakaryocytic) and (2) central (amegakaryocytic) categories. The peripheral group includes (1) idiopathic and (2) secondary (peripheral or hypersplenic) types and (3) thrombotic thrombocytopenic purpura. The central category includes the toxic bone marrow depression group.

Peripheral Megakaryocytic Thrombocytopenic Purpuras: Idiopathic thrombocytopenic purpura. The demonstration by Harrington and his associates, in 1951, of antibodies to platelets in a number of cases of idiopathic thrombocytopenic purpura was a milestone.[608] Much work continues along these lines. Other workers have confirmed the existence of a thrombocytopenic factor.[609] An antiplatelet substance which agglutinates dog, rabbit, and rat platelets, but not those of human patients, was found in the serum of patients with various types of thrombocytopenia.[610] The anti-human-platelet factor is demonstrable by the indirect methods of platelet counting but not by a direct citrate method.[611] A similar factor produces a temporary but significant thrombocytopenia in persons receiving blood from non-thrombocytopenic donors.[612] Platelets injected into persons with idiopathic thrombocytopenic purpura disappear rapidly from the circulation; those injected into patients with secondary thrombocytopenic purpura survive much longer.[613] Platelet survival following transfusion is correlated with duration of improvement in the recipient.[614] The development of antiplatelet substance following repeated transfusions has been suggested as the mechanism producing progressively shorter survival times.[615]

608. Stefanini, M.; Chatterjea, J. B., and Adelson, E.: Immunologic Aspects of Idiopathic Thrombocytopenic Purpura (ITP), abstracted, J. Clin. Invest. **31**:665, 1952.

609. Sprague, C. C.; Harrington, W. J.; Lange, R. D., and Shapleigh, J. B.: Platelet Transfusions and the Pathogenesis of Idiopathic Thrombocytopenic Purpura, J. A. M. A. **150**:1193, 1952.

610. Adelson, E., and Stefanini, M.: Studies on Platelets: IV. Demonstration and Characterization of a Heterologous (Forssman) Platelet Agglutination, Blood **7**:700, 1952.

611. Wilson, S. J.; Eisemann, G., and Chance, J. H.: Plasma "Thrombocytopenic Factor" as Measured by Direct and Indirect Platelet Methods, Proc. Soc. Exper. Biol. & Med. **81**:317, 1952; The Effect of the "Thrombocytopenic Factor" of Idiopathic Thrombocytopenic Purpura on Platelet Levels as Measured by Direct and Indirect Methods, J. Lab. & Clin. Med. **40**:498, 1952.

612. Stefanini, M., and Chatterjea, J. B.: Studies on Platelets: IV. A Thrombocytopenic Factor in Normal Human Blood, Plasma, or Serum, Proc. Soc. Exper. Biol. & Med. **79**:623, 1952.

613. Stefanini, M.; Chatterjea, J. B.; Dameshek, W.; Zamnos, L., and Santiago, E. P.: Studies on Platelets: II. The Effect of Transfusion of Platelet-Rich Polycythemic Blood on the Platelets and Hemostatic Function in "Idiopathic" and "Secondary" Thrombocytopenic Purpura, Blood **7**:53, 1952.

614. Hirsch, E. O., and Gardner, F. H.: The Transfusion of Human Blood Platelets, J. Lab. & Clin. Med. **39**:556, 1952.

615. Stefanini, M.; Dameshek, W., and Adelson, E.: Platelets: VII. Shortened "Platelet Survival Time" and Development of Platelet Agglutinins Following Multiple Platelet Transfusions, Proc. Soc. Exper. Biol. & Med. **81**:230, 1952.

A high titer of heterophile antibody was found in the serum of one patient.[616] Attempts to establish a relation between pulmonary circulation and excessive platelet destruction have failed.[617] Radioisotopic tagging of transfused rabbit platelets allows determination of their survival.[618]

Interest in the prognostic significance of the marrow eosinophilia in idiopathic thrombocytopenic purpura continues.[619] A comparison of marrows from 100 patients with idiopathic thrombocytopenic purpura with those of normal nonallergic subjects revealed no differences in the marrow eosinophile counts.[620]

General summations [621] and the role of the spleen in the removal of circulating platelets have been critically reviewed.[622] Splenectomy remains the treatment of choice [623]; favorable effects are reported in 60 to 90% of the cases. Effective treatment with corticotropin and cortisone is more variable.[624]

Secondary (peripheral or "hypersplenic") thrombocytopenic purpura. This has been reported in a case of tuberculosis,[625] in a male Negro with lupus erythematosus,[626] in infectious mononucleosus,[627] and in two children following mild attacks

616. Stefanini, M., and Adelson, E.: Studies on Platelets: VIII. Heterophile Reaction Due to Forssman Antibody in Patients with Idiopathic and Secondary Thrombocytopenic Purpura, Am. J. Clin. Path. **22**:1164, 1952.

617. Stefanini, M.; Chatterjea, J. B., and Dameshek, W.: Studies on Platelets: V. Observations on the Removal by the Pulmonary Circulation of Platelets Injected into Patients with Idiopathic Thrombocytopenic Purpura, J. Lab. & Clin. Med. **39**:865, 1952.

618. Mueller, J. F.: Some Studies Concerning the Pathologic Physiology of the Mammalian Blood Platelet Utilizing P^{32} Tagged Rabbit Platelets, abstracted, J. Lab. & Clin. Med. **40**:925, 1952.

619. Schwartz, S. O.: Is Marrow Eosinophilia a Valid Yardstick for Splenectomy in Thrombocytopenic Purpura? Illinois M. J. **101**:309, 1952.

620. Presley, S. J.; Best, W. R., and Limarzi, L. R.: Bone Marrow in Idiopathic Thrombocytopenic Purpura, J. Lab. & Clin. Med. **40**:503, 1952.

621. Dameshek, W.: "Idiopathic" Thrombocytopenic Purpura, Quart. Bull. Northwestern Univ. M. School. **26**:1, 1952.

622. Stefanini, M.; Chatterjea, J. B.; Dameshek, W.; Welch, C. S., and Swenson, O.: Studies on Platelets: III. The Absence of "Selective Sequestration" and Destruction of Platelets by the Spleen in "Idiopathic" Thrombocytopenic Purpura, Blood **7**:289, 1952. Stefanini, M.: Recent Observations on the Pathogenetic Mechanism of Idiopathic Thrombocytopenic Purpura, J. Mt. Sinai Hosp. **19**:452, 1952.

623. Hanlon, D. G.: Some Problems in Hematology: Some Problems in the Management and Pathogenesis of Idiopathic Thrombocytopenic Purpura, Proc. Staff Meet., Mayo Clin. **27**:273, 1952. Schenken, J. R.: Primary Thrombocytopenic Purpura, New Orleans M. & S. J. **154**:477, 1952. Giannini, A. P.: Splenectomy for the Fulminating Episode of Essential Thrombocytopenic Purpura, Surg., Gynec. & Obst. **94**:229, 1952.

624. Davidson, Girdwood, and Swan.[108c] Faloon, Greene, and Lozner.[116a] Wilson and Eisemann.[116c] Dameshek.[621]

625. Ellman, P., and Johnson, J. H. P.: Tuberculosis and Purpura, Brit. J. Tuberc. **46**:214, 1952.

626. Friedman, I. A.; Kleinschmidt, W. H., and Schwartz, S. O.: Disseminated Lupus Erythematosus with Severe Thrombocytopenia in a Negro Male, Illinois M. J. **101**:212, 1952.

627. Butterworth, C. E., Jr.; Riser, W. H., Jr., and Frommeyer, W. B., Jr.: The Simultaneous Occurrence of Thrombocytopenic Purpura and Acute Infectious Mononucleosis, Phi Chi Quart. **49**:514, 1952.

of measles.[628] Its occurrence in pregnancy has been reviewed.[128a] In one woman purpura occurred during two successive pregnancies.[128b] Thrombocytopenia has also been associated with sarcoidosis of the spleen.[629]

Thrombotic thrombocytopenic purpura. Reviews of thrombotic thrombocytopenic purpura are numerous, particularly in the European literature.[630] It is clinically characterized by an acute pyrexal course, with thrombocytopenic purpura, hemolytic anemia, neurologic signs, and an invariably fatal termination. There are widespread hyaline thromboses of the smaller vessels. These may be demonstrated before death in gum biopsy examinations.

Toxic (Central) Thrombocytopenic Purpura: The "amegakaryocytic" group is discussed on page 365.

THE RETICULOENDOTHELIUM SYSTEM

Experimental Studies.—The role of the reticuloendothelial system in vitamin A metabolism has been correlated with the nephrotic syndrome.[631] Macrophages labeled with thorium dioxide move in the blood in significant numbers, and their pattern of movement has been outlined.[632]

The Reticuloendothelioses.—These include Gaucher's disease, Nieman-Pick disease,[633] Hand-Schüller-Christian disease, Letterer-Siwe disease, eosinophilic granuloma, and several less well-defined clinical entities, and they may frequently resemble leukemia. Their neoplastic aspects have been discussed.[634]

Reports on Gaucher's disease are concerned with diagnosis by splenic puncture,[635] its occurrence in a Negro [636] and in pregnancy,[637] and citation of a case with initial symptoms in the shoulder joint.[638]

628. Fisher, O. D., and Kraszewski, T. M.: Thrombocytopenic Purpura Following Measles, Arch. Dis. Childhood **27**:144, 1952.

629. Schrijver, H., and Schillings, P. H. M.: Thrombocytopenic Purpura with Sarcoidosis, Cured after Splenectomy, Acta med. scandinav. **144**:213, 1952.

630. Symmers, W. S. C.: Thrombotic Microangiopathic Haemolytic Anaemia (Thrombotic Microangiopathy), Brit. M. J. **2**:897, 1952. Blackman, N. S.; Cohen, B. M., and Watson, J.: Thrombotic Thrombopenic Purpura, J. A. M. A. **148**:546, 1952. Rackow, F.; Steingold, L., and Wood, J. H. F.: Thrombotic Thrombocytopenic Purpura, Acta med. scandinav. **143**:137, 1952. Barondess, J. A.: Thrombotic Thrombocytopenic Purpura, Am. J. Med. **13**:294, 1952. Cooper, T.; Stickney, J. M.; Pease, G. L., and Bennett, W. A.: Thrombotic Thrombocytopenic Purpura: Confirmation of Clinical Diagnosis by Bone Marrow Aspiration, ibid. **13**:374, 1952. Gendel, B. R.; Young, J. M., and Kraus, A. P.: Thrombotic Thrombocytopenic Purpura, ibid. **13**:3, 1952. Adelson and Stefanini.[610]

631. The Reticuloendothelial System in Vitamin A Metabolism, Nutrition Rev. **10**:306, 1952.

632. Easton, T. W.: The Role of Macrophage Movements in the Transport and Elimination of Intravenous Thorium Dioxide in Mice, Am. J. Anat. **90**:1, 1952.

633. Videbaek, A.: Another Case of Niemann-Pick's Disease Observed in Denmark, Acta pædiat. **41**:355, 1952.

634. Zeldenrust, J.: Die Pathologie der Retikulosen, Acta haemat. **7**:161, 1952.

635. Reddy, D. G., and Anguli, V. C.: Gaucher Splenomegaly: Diagnosed by Spleen Puncture Before Operation, Indian M. Gaz. **87**:358, 1952.

636. Stansbury, F., and Schwartz, S. O.: Gaucher's Disease in the Negro, Illinois M. J. **101**:145, 1952.

637. Elliott, J. F.: Gaucher's Disease: A Case Complicated by Pregnancy, Canad. M. A. J. **66**:166, 1952.

638. James, N. E.: Gaucher's Disease, J. Bone & Joint Surg. **34**:464, 1952.

Nitrogen mustard therapy produces temporary remissions in some cases of reticuloendotheliosis.[639] Roentgen radiation is most effective in localized cases. The treatment of generalized cases is aimed at conserving the radiation tolerance of the patient.[640] Cortisone produces transient improvement in Hand-Schüller-Christian disease.[641]

THE SPLEEN

General Investigations.—In investigations on normal and splenectomized rabbits[642] the spleen was found to participate in antibody production primarily in the initial rise and in the anamnestic response. Nonsplenic sites of antibody production partially compensate in rabbits splenectomized 51 days or more. Thus, the question of increased susceptibility to infection in splenectomized persons was again revived. Septicemia or meningococcemia developed six weeks to three years after operation in five children who had undergone splenectomy while less than six months of age.[643] These striking observations suggest the importance of a careful review of the experience of other groups.

The increased histamine content of the splenic depot blood is thought to participate in maintenance of phagocytic function.[644] Extirpation of the spleen after venesection lowers the reticulocyte response of the marrow.[645]

Carcinoma metastases to the spleen occurred in 2.3% of cases from primary lesions in the bronchus, breast, skin (malignant melanoma), and cervix, in that order of frequency.[646]

Hypersplenism.—Discussions of the primary and secondary hypersplenic syndromes are interspersed throughout the review and to avoid repetition reference to these is suggested (see pages 401, 408, and 423). Summary reviews have been made of current concepts, criteria for diagnosis, and treatment.[647] Although some objection has been voiced concerning the epinephrine test,[648] if properly used it is valuable as

639. Blattner, R. J.: Reticuloendotheliosis, Postgrad. Med. **12**:427, 1952.

640. Tod, M. C.: The Reticuloses and Lymphoreticular Sarcomas from the Radiotherapist's Point of View, Edinburgh M. J. **59**:457, 1952.

641. Karlen, K. H.: A Case of the Hand-Schüller-Christian Disease Treated with Cortisone, Acta pædiat. **41**:282, 1952.

642. Taliaferro, W. H., and Taliaferro, L. G.: The Role of the Spleen and the Dynamics of Hemolysin Production in Homologous Anamnesis, J. Infect. Dis. **90**:205, 1952.

643. King, H., and Shumacker, H. B., Jr.: Splenic Studies: I. Susceptibility to Infection After Splenectomy Performed in Infancy, Ann. Surg. **136**:239, 1952.

644. Ludány, G.; Obál, F.; Balogh, J., and Szántó, T.: Histamingehalt des Depotblutes der Milz, Arch. internat. pharmacodyn. **89**:15, 1952.

645. Ruhenstroth-Bauer, G., and Maier, K. H.: Versuche zum Nachweis eines spezifischen erythropoetischen Hormons, Arch. exper. Path. u. Pharmakol. **214**:464, 1952.

646. Hirst, A. E., Jr., and Bullock, W. K.: Metastatic Carcinoma of the Spleen, Am. J. M. Sc. **233**:414, 1952.

647. (*a*) Schatken, R. V.: Hypersplenism: A Review and Case Report, Ann. Surg. **135**:530, 1952. (*b*) Evans, T. S., and Doan, C.: État actuel du diagnostic des syndromes d'hypersplénisme, Rev. hémat. **7**:332, 1952. (*c*) Rottino, Hoffman, and Albaum.[584]

648. Groisser, V., and Ruberman, W.: A Study of the Mechanisms in the "Hypersplenic Syndrome", Proceedings American Federation Clinical Research, National Meeting, Atlantic City, N. J., May 4, 1952.

a confirmatory diagnostic tool for dyssplenism.[647a] Other diagnostic phases reviewed are x-ray visualization of the spleen [649] and examination of tissue sections for Malpighian corpuscles with prominent marginal zones.[650]

An interesting case of Felty's syndrome was associated with a panhemocytopenia. The increase in destruction of the circulating formed elements was not confined to the spleen but also involved the generalized reticuloendothelium system. A unique feature was the presence of a circulating leucolytic agent.[651] Abdominal tuberculosis has also resulted in secondary hypersplenic syndromes.[652] A saline extract of the spleen from a patient with hypersplenic panhemocytopenia was injected subcutaneously into rabbits and resulted in a similar panhemocytopenia.[653]

The value of splenectomy in hypersplenism has again been confirmed.[654] Failure to induce a reequilibration may be due to one of several factors: (1) to a wrong diagnosis, (2) to accessory spleens,[655] or (3) to such massive destruction by the entire reticuloendothelial system that removal of the splenic components is just not sufficient. Accessory spleens may be demonstrated roentgenologically with thorium dioxide (Thorotrast) localization.[656] Two additional cases of ectopic accessory spleens in the scrotum have been noted.[657]

Extramedullary Hematopoiesis.—This is regarded generally as a compensatory mechanism and may be associated with a number of disturbances that interfere with adequate marrow production. Splenic myeloid metaplasia is characterized by hepatosplenomegaly and a varying erythroblastic-leukemoid blood reaction.[658] Diagnosis is most direct by splenic biopsy. Splenectomy is contraindicated.[658b] The theory that this syndrome is primarily of splenic origin, with secondary marrow participation has been proposed.[659] Hematopoiesis in primary and metastatic sites of liver cancer in an infant has been reported.[660]

649. Kahler, O. H.: Beitrag zur Beurteilung der Milz bei der Röntgenuntersuchung, Deutsche med. Wchnschr. **77**:363, 1952.

650. Leffler, R. J.: The Spleen in Hypersplenism, Am. J. Path. **28**:303, 1952.

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Case Reports

GUILLAIN-BARRÉ SYNDROME IN INFECTIOUS MONONUCLEOSIS

Report of a Case with Recovery Following Administration of Cortisone

MARSHALL J. FIESE, M.D.
STEPHEN CHEU, M.D.
AND
JEROME RADDING, M.D.
FRESNO, CALIF.

THE PROTEAN manifestations of infectious mononucleosis include various neurological syndromes, most commonly a type of lymphocytic meningitis.[1] The Guillain-Barré syndrome is a rare and potentially serious complication. Although an exact enumeration of previously reported cases is difficult because varying diagnostic criteria were used, 14 probable examples of the Guillain-Barré syndrome in infectious mononucleosis may be cited [2] (Table). The 15th case, herein reported,

From the Medical Service, Veterans Administration Hospital, Fresno, and the Department of Medicine, Stanford University School of Medicine, San Francisco.

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2. Zohman, B. L., and Silverman, E. G.: Infectious Mononucleosis and Encephalomyelitis, Ann. Int. Med. **16**:1233 (June) 1942. Hiller, R. I., and Fox, M. J.: Infectious Neuronitis Associated with Infectious Mononucleosis, Marquette M. Rev. **7**:152 (Feb.) 1943. Coogan, T. J.; Martinson, D. L., and Mathews, W. H.: Neurological Symptoms of Infectious Mononucleosis, Illinois M. J. **87**:296 (June) 1945. Slade, J. de R.: Involvement of the Central Nervous System in Infectious Mononucleosis: A Report of Two Cases, New England J. Med. **234**:753 (June 6) 1946. Geliebter, S.: Acute Infectious Mononucleosis Complicated by Encephalomyelitis, Lancet **2**:753 (Nov. 23) 1946. Ricker, W.; Blumberg, A.; Peters, C. H., and Widerman, A.: The Association of the Guillain-Barré Syndrome with Infectious Mononucleosis, with a Report of Two Fatal Cases, Blood **2**:217 (May) 1947. Peters, C. H.; Widerman, A.; Blumberg, A., and Ricker, W. A., Jr.: Neurologic Manifestations of Infections Mononucleosis, with Special Reference to the Guillain-Barré Syndrome, Arch. Int. Med. **80**: 366 (Sept.) 1947. Haymaker, W., and Kernohan, J. W.: The Landry-Guillain-Barré Syndrome: A Clinicopathologic Report of 50 Fatal Cases and a Critique of the Literature, Medicine **28**:59 (Feb.) 1949. Custer, R. P., and Smith, E. B.: The Pathology of Infectious Mononucleosis, Blood **3**:830 (Aug.) 1948. Dolgopol, V. B., and Husson, G. S.: Infectious Mononucleosis with Neurologic Complications: Report of a Fatal Case, Arch. Int. Med. **83**:179 (Feb.) 1949. Graham, S. D.; Schwartz, W. H., and Chapman, W. L.: Infectious Neuronitis Complicating Infectious Mononucleosis, U. S. Nav. M. Bull. **49**:914 (Sept.-Oct.) 1949. Kløvstad, O.: The Guillain-Barré Syndrome in Infectious Mononucleosis, Acta med. scandinav. **138**:67, 1950. Kløvstad, O., and Vinje, T. L.: Infectious Mononucleosis with Symptoms of Involvement of the Central Nervous System, Nord. med. **43**:795 (May) 1950. Creaturo, E.: Infectious Mononucleosis and Polyneuritis (Guillain-Barré Syndrome): Report of a Case of Facial Diplegia Treated with 2, 3 Dimercaptopropanol (BAL), J. A. M. A. **143**:234 (May 20)

(Footnote continued on next page)

is unusual for two reasons: (1) the patient was by far the oldest recorded and (2) recovery coincided with the administration of cortisone. Although cortisone has been reported to be of value in the treatment of other types of the Guillain-Barré syndrome,[3] its use has not previously been described in polyneuritis due to infectious mononucleosis.

REPORT OF CASE

A white male carpenter, aged 58 years, entered the Fresno Veterans Administration Hospital on April 5, 1952, because of increasing weakness of the legs and arms.

Two months previously he had suffered a sore throat and a dry cough. A week later, it became difficult to swallow solid food and fluids were often regurgitated through the nose. His hearing became impaired, particularly on the right. He began to see double. His gait became unsteady and staggering; he could not walk in the dark. Tingling and numbness spread up the extremities and trunk from the feet and hands. He burned his fingers with a cigarette without

Previously Reported Cases of Guillain-Barré Syndrome Complicating Infectious Mononucleosis

Authors	Cases, No.
Zohman and Silverman	1
Hiller and Fox	1
Coogan and others	1
Slade	1
Gellebter	1
Ricker and others	2*
Dolgopol and Husson	1
Graham and others	1
Kløvstad	1
Creaturo	1
Silversides and Richardson	1
Owen	1
Garvin	1
Total	14

* These two fatal cases, from the Army Institute of Pathology, were also reported by Peters and others, Haymaker and Kernohan, and Custer and Smith. Some authors (Silversides and Richardson, and Garvin) have counted these cases twice, giving an erroneous total number of cases and deaths.

feeling it. His legs and arms became progressively weaker. For a while he could walk with a cane, and then not at all. He became too weak to stand, then too weak to sit up in bed, and finally he could neither move himself in bed nor pick up anything with his hands. He lost 20 lb. (9 kg.) in a month.

Physical Examination.—The patient was a well-developed, fairly well-nourished man lying helplessly in bed. He was cooperative and mentally clear. The cervical lymph nodes were

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3. Stillman, J. S., and Ganong, W. F.: The Guillain-Barré Syndrome: Report of a Case Treated with ACTH and Cortisone, New England J. Med. **246**:293 (Feb. 21) 1952. Seltzer, H. S.; Lichty, D. E., and Conn, J. W.: Case of Guillain-Barré Syndrome (Infectious Polyneuritis) with Apparent Response to ACTH, Univ. Michigan M. Bull. **18**:27 (Jan.) 1952. Newey, J. A., and Lubin, R. I.: Corticotropin (ACTH) Therapy in Guillain-Barré Syndrome, J. A. M. A. **152**:137 (May 9) 1953. Blood, A.; Locke, W., and Carabasi, R.: Guillain-Barré Syndrome Treated with Corticotropin (ACTH), ibid. **152**:139 (May 9) 1953.

moderately enlarged but were not tender. The lungs were somewhat emphysematous. Heart sounds were distant. Blood pressure was 128 systolic and 74 diastolic.

Neurological Examination.—The pupils were round and equal, and reacted to light and in accommodation. There was no demonstrable strabismus, although the patient complained of diplopia. Nystagmus occurred on lateral gaze. Bone conduction was better than air conduction on the right. He could swallow only with difficulty.

There was a complete loss of the sensations of light touch, vibration, and position below the level of the umbilicus and in the wrists and hands. Stereognostic sensation was lost. The patient could neither stand nor sit up unaided. The calf muscles were atrophic. The legs and hands were symmetrically weak but not completely paralyzed. Muscle coordination was poor. Responses to the finger to nose test and heel to knee test were inaccurate. Past pointing was evident. The biceps, triceps, superficial abdominal, knee, and ankle reflexes could not be elicited.

Laboratory Studies.—The hematocrit reading was 46 volumes %, the hemoglobin 14.8 gm. per 100 cc., and the white cell count 7,750 per cubic millimeter. The differential cell count, when first determined, two months after the onset of the disease, was 53% neutrophiles, 46% lymphocytes, and 1% monocytes. No unusual lymphocytes were noted at that late date. The urine was normal. The serological test for syphilis was negative. No cells were found in the spinal fluid on repeated search. The spinal fluid protein, originally 97 mg. per 100 cc., later rose to 200 mg. per 100 cc. The colloidal gold sol curve was 0000032100. A throat culture showed no Corynebacterium diphtheriae. The serum heterophile antibody titer was positive in a dilution of 1 to 1,792.

Course in the Hospital.—With symptomatic therapy alone the patient became progressively weaker for 10 days. On the 11th hospital day, treatment with cortisone acetate was begun, 300 mg. the first day, 200 mg. the second day, and 100 mg. daily thereafter for two months. Within three days the patient was stronger in the knees and trunk and could use his hands better. A sensation of tingling reappeared in the hands and feet. Within three more days vibratory sense returned in the extremities. There was steady improvement thereafter. In a month he could walk again. He regained his lost weight. Three months after entry all neurological signs and symptoms had disappeared except slight numbness in the soles. Deep tendon reflexes became normal, and the extremities became strong. The heterophile antibody titer decreased to 1 to 56, and the spinal fluid protein fell to 65 mg. per 100 cc.

COMMENT

Infectious mononucleosis and the Guillain-Barré syndrome are usually diseases of youth. Bernstein, in 1950, reviewed the 46 cases of all types of neurological complications of infectious mononucleosis then reported.[4] Ages ranged from 2 to 38 years, the average being 22.8. The 14 previously reported patients with the Guillain-Barré syndrome complicating infectious mononucleosis range in age from 6 to 36, the average being 20.4 . Our patient, aged 58, is by far the oldest, not only of those with Guillain-Barré syndrome but also of those with any type of neurological complication.

As far as we know, this is the first time that cortisone has been reported in the treatment of the Guillain-Barré syndrome due to infectious mononucleosis. Because the disease is usually self limited, it is impossible to be sure that cortisone had anything to do with this patient's recovery. Indeed, his total course was similar to that of untreated patients. However, a spontaneous recovery was by no means assured, for 3 of the 14 reported cases of Guillain-Barré syndrome complicating

4. Bernstein, T. C., and Wolff, H. G.: Involvement of the Nervous System in Infectious Mononucleosis, Ann. Int. Med. **33**:1120 (Nov.) 1950.

infectious mononucleosis have been fatal. Furthermore, symptoms progressed relentlessly until cortisone was administered, whereas recovery began immediately thereafter. Although the improvement may have been a coincidence, the possibility of its causal relationship to the use of cortisone is strong enough to warrant further investigation.

SUMMARY

Infectious mononucleosis in a 56-year-old man was followed by a severe polyneuritis of the Guillain-Barré type. His case is the 15th such to be reported. He was by far the oldest. Recovery was coincident with the administration of cortisone. As far as we know, this is the first time the use of cortisone has been reported in the Guillain-Barré syndrome due to infectious mononucleosis.

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SHEEHAN'S SYNDROME (POSTPARTUM PANHYPOPITUITARISM)

Report of a Case and Comment on Clinical Management

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A CASE of Sheehan's syndrome (postpartum panhypopituitarism) is presented, with observations on treatment. The patient showed evidence of secondary thyroid, adrenal, and gonadal failure. Combined stimulation and replacement therapy restored the patient to health.

Mrs. E. H., age 44, was admitted to St. Joseph's Hospital, Vancouver, Wash., on Oct. 10, and was discharged on Nov. 8, 1952.

The chief complaints, as given by the patient's mother, were nausea and vomiting, drowsiness, extreme weakness, and mental confusion.

The present illness began about five months before admission, when the patient's mother noted that she was becoming irritable, was easily upset by small troubles, and had a capricious appetite. She had always been good natured before this time. Her dentist had refused to extract her carious teeth unless she would take thyroid and iron; thyroid had been advised a year before but the patient had taken it very haphazardly and finally stopped taking it in the spring of 1952.

About five weeks before admission the patient became worse. She began to vomit, lost her appetite, and frequently had spells of hiccups and belching. There was a brief episode of right frontal head pain, redness, and swelling lasting for three days. About this time some cough with white sputum and fever, to 101 F., without chills, also developed. Four weeks before admission a physician in another city examined her for complaints of weakness, anorexia, weight loss, nausea, vomiting, and persistent cough. This doctor found the blood pressure in her right arm to be 90/86 and in the left arm, 80/74. The skin was dry; there were left basilar rales and a pulse rate of 60, with weak cardiac pulsations of small amplitude found on fluoroscopy. An electrocardiogram showed low voltage, with inversion of all T waves. A blood count was within normal limits and urinalysis showed no abnormalities, but the sedimentation rate was 7 and 44. Blood cholesterol measured 410 mg. per 100 cc., and the basal metabolism was —26%. The patient was advised to take 1/10 grain (6 mg.) of thyroid daily. On this regimen she did not improve, but became weaker, lost weight, vomited more often, became delirious and disoriented, and one week before admission began to imagine that an atom bomb was in the room and that airplanes were flying around her bed.

Personal History.—The patient had had no serious infectious disease or operations. While she was living on a farm in 1941, some cows had to be killed because of brucellosis, but the patient never had this disease. General questioning revealed no ear, nose, or throat complaints; she had had some chronic cough with white sputum for about a year but never any hemoptysis and a survey chest film made in 1951 was pronounced normal. There were no cardiac, gastrointestinal, urinary, or neuromuscular complaints before the present illness. Menarche was at age 17; the patient was the only one of seven sisters to start menstruating at this late age. Her periods were normal once she started, however. She had six pregnancies; the first three were normal. The fourth (1935, age 27) was complicated by toxemia (preeclampsia) and terminated in a stillbirth near term. The labor was apparently induced to avoid eclampsia. The patient lost a great deal of blood during this procedure, and her husband was told that she couldn't live unless transfusions were given. She had three, and slowly recovered. She did not lactate after this pregnancy, and menses stopped except for two periods, during which she again became pregnant, for the fifth time (1937, age 29). This pregnancy was uneventful, and the child is living and well at age 15. After this pregnancy the patient failed to lactate and the menses did not return

except at one time, during which cycle she became pregnant for the last time and delivered her youngest child, who is now living and well at age 13. After this pregnancy her pubic hair did not grow back, and the axillary hair began to disappear. There have been no menstrual periods following this birth, the patient being 31 years old at the time her periods stopped entirely.

Family History.—The father died of coronary disease; many of his brothers and his father died of the same ailment. The mother is living at age 57 but for about one year has had recurrent bouts of left lower lobe pleurisy with fever and copious green sputum. No tubercle bacilli have ever been found. There is no familial tuberculosis, heart disease, or diabetes.

Physical Examination.—The patient was a drowsy, weak, disoriented, hallucinating, poorly nourished woman who looked older than her stated age. Temperature was 99 F., pulse rate 60 to 80, respirations 20, and blood pressure 70/60. The skin was dry and flabby. The hair was fine, with some thinning of the eyebrows at the lateral margins. There was no axillary or pubic hair. There was severe dental caries. The breasts were flabby and atrophic. There was diminished breathing at the left lung base, with scattered rales in this region. A marked third heart sound was heard in middiastole. There was atrophic vaginal mucosa, a small soft cervix, and small uterus. The deep reflexes were hypoactive. The remainder of a complete physical examination showed no abnormalities. There was no abnormal skin pigmentation, and there were no spots on the oral mucosa.

Laboratory Studies.—Admission blood cell count showed 10.6 gm. of hemoglobin, 3,560,000 red blood cells, and 3,250 white blood cells, with 52% polymorphonuclear, 46% lymphocytic, and 2% "stab" cells. There was a trace of albumin in the urine and from 10 to 20 white cells per high-power field. On the fourth day, results of chemical study of the blood, in milligrams per 100 cc., were as follows: fasting blood sugar 67, cholesterol 126, calcium 11, phosphorus 1.8, urea nitrogen 6, chlorides 490 (as sodium chloride, normal being 575 to 630). Alkaline phosphatase was 0.4 King-Armstrong units and CO_2-combining power 75 volumes per cent. Subsequent laboratory studies showed gradual return to normal of the blood sugar, chlorides, and cell counts after replacement therapy with corticotropin (ACTH), as described below.

An electrocardiogram on two occasions showed low voltage (3 mv. maximum in the limb leads), all T waves inverted, and an R-T interval of 0.48 second, with a heart rate of 50.

Chest x-ray showed left basilar hazy infiltration which cleared entirely after three weeks. A skull x-ray series showed no abnormalities.

A Thorn test, done after two days of corticotropin therapy (60 mg. a day) showed an initial eosinophile count of 77, with a count of 22 four hours after injection of an extra dose of 25 mg. of corticotropin. This is a normal response (greater than 50% fall) and indicates adequate adrenal response to pituitary stimulation, thus ruling out primary adrenal failure.

First and second strength endodermal tuberculin tests were negative.

Course.—For three days, with supportive therapy of intravenous dextrose and isotonic sodium chloride solution, oxygen, caffeine, vitamins, and Ringer's solution, the patient remained very weak, drowsy and confused and was sometimes cyanotic and apprehensive. She vomited several times, ate poorly, and picked at the bed clothes. Hallucinations continued. The blood pressure went as low as 60/50 on one occasion. On the fourth day use of corticotropin, 10 mg. every four hours, was started. On the next day thyroid, 1/10 grain (6 mg.), was added, and a high salt, high calorie diet was begun. The patient began to improve and a good appetite developed; the hallucinations disappeared and she became alert and cheerful though still very weak. We tried cortisone, 12.5 mg. twice daily, on the seventh day, with testosterone, 10 mg., and 1 gm. of salt with each meal. On this medication she became edematous; so corticotropin was resumed on the 10th day. A daily dose of 3 gm. potassium chloride and 2.5 mg. desoxycorticosterone was added on the 15th day. By the 12th day she was able to sit in a chair and was rational and feeling stronger. From this time improvement was rapid; the blood pressure reached 104/80 on the 18th day. By the 22nd day the fasting blood sugar was 90 mg. and the chloride (as sodium chloride) was 580 mg. The patient was able to walk about and was discharged on the 28th hospital day.

After discharge she was seen twice weekly in the office. She improved steadily and is now on this medication: corticotropin gel, 10 mg. every third day; 1¼ grains (75 mg.) of thyroid, 2.5 mg. desoxycorticosterone acetate, and 3 gm. of postassium chloride per day. Her blood

pressure remains around 108 to 120 systolic, and she feels, acts, and looks like an entirely normal person. The electrocardiogram two months after discharge (Fig.) showed some improvement, in that the T waves were less deeply inverted and voltage had improved a little (maximum 4.5 mm. in Lead I), but only TaV_L and TV were slightly above the baseline, the rest being isoelectric or inverted.

COMMENT

A paraphrase of Sheehan's original summary [1] of a "typical case" will show how closely the present patient corresponds to his description.

The original (pituitary) necrosis occurs at a delivery invariably complicated by collapse, usually as a result of severe hemorrhage. Following this the patient fails to lactate in the puerperium and sometimes shows hypoglycemia. The uterus superinvolutes, the external genitalia atrophy. Menses fail to return and libido is absent. There is gradual loss of axillary and pubic hair. The patient is apathetic and dull, cannot do her housework, is very sensitive to cold, and may look myxedematous or prematurely senile. The blood pressure tends to be low, the basal metabolic rate around minus 25 per cent; there is a hypochromic anemia and sometimes an eosinophilic leucocytosis. Blood cholesterol may be slightly raised and blood sugar low.

After 10, 20, or 30 years the patient may become more typically myxedematous and develop mental changes, anorexia, and weight loss. The anemia may become hyperchromic; the basal metabolic rate may fall to minus 35 per cent. Finally, usually as a result of intermittent illness or severe anorexia, the patient passes into coma and dies, usually with hypoglycemia. The pathologic changes are pituitary necrosis and scarring, atrophy of the adrenal cortex, an atrophied fibrous thyroid, shrunken uterus and ovaries, and small viscera.

Diagnosis may be difficult, since the disease may mimic a psychosis, anorexia nervosa, primary hypothyroidism, Addison's disease, or a pituitary tumor. However, tests available in the average hospital will usually serve to make the diagnosis without the need for gonadotrophin or 17-ketosteroid studies. I refer especially to skull x-rays; electrocardiogram; basal metabolism test; determination of blood sugar, chlorides, urea nitrogen, cholesterol, and cell counts, and the Thorn eosinophile test. It is important to distinguish primary hypothyroidism from the secondary type due to pituitary failure, because thyroid therapy in the latter "may precipitate a fatal adrenal crisis due to the secondary adrenal cortical insufficiency which is almost always present." [2] Secondary or pituitary myxedema should be suspected if the patient shows atrophy of the sex organs, loss of axillary and pubic hair, absent libido, and marked persistent hypotension.[2]

Addison's disease can be differentiated by the Thorn eosinophile test; atrophied adrenals will not respond to stimulation by corticotropin or epinephrine. Patients with Sheehan's disease, although having hypochloremia, hypoglycemia, and hypotension, rarely show the typical Addisonian pigmentation.

Pituitary tumors usually cause visual disturbances, headaches, and erosion of the sella turcica visible on x-ray. Israel and Conston [3] have presented an excellent outline of diagnostic aids to the recognition of subclinical hypopituitarism in their article on Sheehan's syndrome as a cause of sudden death.

The treatment of panhypopituitarism has become much simpler and more exact since corticotropin and cortisone have been introduced for general clinical use.

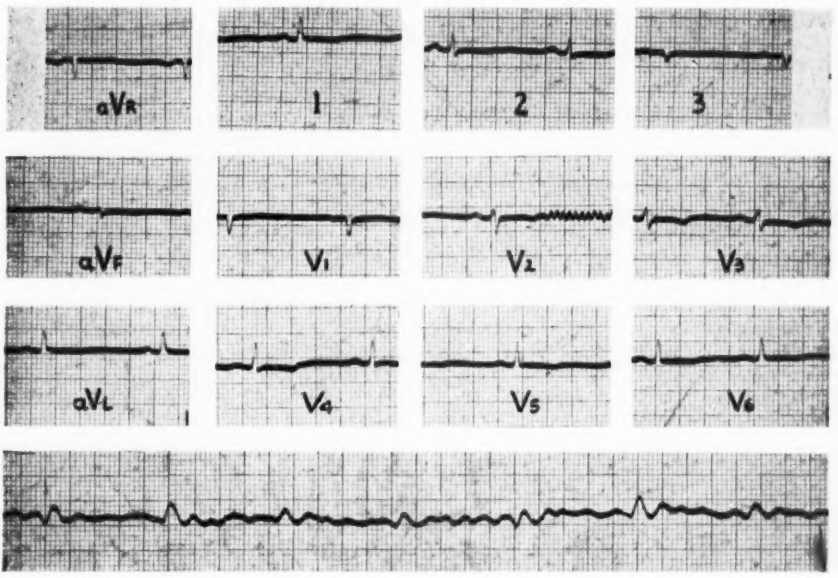
1. Sheehan, H. L.: Post-Partum Necrosis of Anterior Pituitary, J. Path. & Bact. **45**:189-214 (July) 1937; Simmonds's Disease Due to Post-Partum Necrosis of the Anterior Pituitary, Quart. J. Med. **8**:277-309 (Oct.) 1939.

2. Harrison, T. L., and others, Editors: Internal Medicine, Philadelphia, The Blakiston Company, 1950.

3. Israel, S. L., and Conston, A. S.: Unrecognized Pituitary Necrosis (Sheehan's Syndrome): A Cause of Sudden Death, J. A. M. A. **148**:189-193 (Jan. 19) 1952.

Either may be used. Cortisone and desoxycorticosterone acetate (DOCA) are probably more practical, if one watches for salt retention and edema and supplements the diet with added potassium to avoid the hypochloremic hypokalemic alkalosis which may develop. Some patients develop resistance to corticotropin, but this will not occur with the newer highly purified preparations. There is no single satisfactory substitute for the patient's own pituitary stimulation to the thyroid, adrenal, and gonadal activities, so thyroid extract with suitable estrogen and/or androgen preparations must be used. The patient I have reported is at the age when normal menopause would be expected, so no estrogens have been given. Methyltestosterone is useful for its nitrogen-retaining, anabolic effects.

So far this patient has done well, and there have been no undesirable side effects from corticotropin except a troublesome insomnia while she was taking 15 mg. of



Electrocardiogram and ballistocardiogram taken March, 1953.

corticotropin a day. This disappeared when she reduced the dose to 15 mg. every other day. Although she has had no evidence of tuberculosis (negative second strength tuberculin tests), chest films should be taken once or twice a year.

Her electrocardiogram (March, 1953) shows some return of T waves toward the baseline, but they are still inverted, except for Lead III, which is isoelectric. The voltage is still low, but is considerably improved from the original tracing. With increased thyroid dosage there may be a return to normal, but with the family history of coronary disease one wonders whether there is some permanent change perhaps not related to hypothyroidism. A ballistocardiogram reveals marked low amplitude and a suggestive M-shaped complex (Figure), which may be seen in coronary disease.

Dr. Warren S. Shepperd, of Camas, Wash., gave permission to use the hospital data. Dr. Huldrick Kammer, of Portland, Ore., made suggestions for management of this case.

Correspondence

PROF. MAX NEUBURGER

To the Editor:—I am calling attention to the fact that Dec. 8, 1953, is the eighty-fifth birthday of the veteran of medical history, Prof. Max Neuburger. He was Professor of Medical History at the University of Vienna from 1904 to 1934. In 1939 he was elected Professor of Medical History at the Chicago Medical College, but owing to war conditions he was unable to come to the United States. In 1948 he came to the United States and settled in Buffalo, N. Y. In 1952, on the invitation of the Austrian government, he returned to Vienna.

Professor Neuburger is the author of the classic *Geschichte der Medizin* (two volumes, 1906-1910) and the author of about two hundred original articles on his specialty. Many of his essays on medical history appeared in *Medical Life,* New York, and *Bulletin of the History of Medicine,* Baltimore. He was the only author to describe the medicine of Josephus Flavius (A. D. 33-95). His publications for a period of fifty-eight years (1892-1950) enriched the literature of medical history. Many of his pupils are now teachers of the history of medicine in various parts of the world. Professor Neuburger was the founder of the Institute of Medical History and the Museum at the Vienna Medical School.

I join with his many disciples and admirers in extending most cordial wishes to Professor Neuburger.

SOLOMON R. KAGAN, M.D., H.L.D., Sc.D.,
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Obituaries

NEWELL C. GILBERT, M.D.
1881-1953

Dr. Newell C. Gilbert, a member of the editorial board of the A. M. A. ARCHIVES OF INTERNAL MEDICINE from 1932 to Jan. 1, 1950, and Chief Editor from 1937 until the time of his retirement, died in St. Joseph's Hospital, Milwaukee, Aug. 1, 1953. He had been removed from his summer home at Pentwater, Mich.

Dr. Gilbert was born in Clinton, Ill., in 1881 and graduated from the University of Wisconsin in 1903. His medical training, including a M.S. degree, was obtained at Northwestern University School of Medicine, after which he served continuously on the Northwestern faculty until his retirement, three years ago. For many years he had been Professor of Medicine and Chairman of the Department of Internal Medicine along with his duties on the ARCHIVES. His internship was served at St. Luke's Hospital, Chicago, and he was appointed as a regular staff member of this institution in 1916. For many years prior to his retirement he had been head of the department of internal medicine at St. Luke's.

In World War I he was a captain and then a major in the medical corps, retiring with the reserve rank of lieutenant colonel.

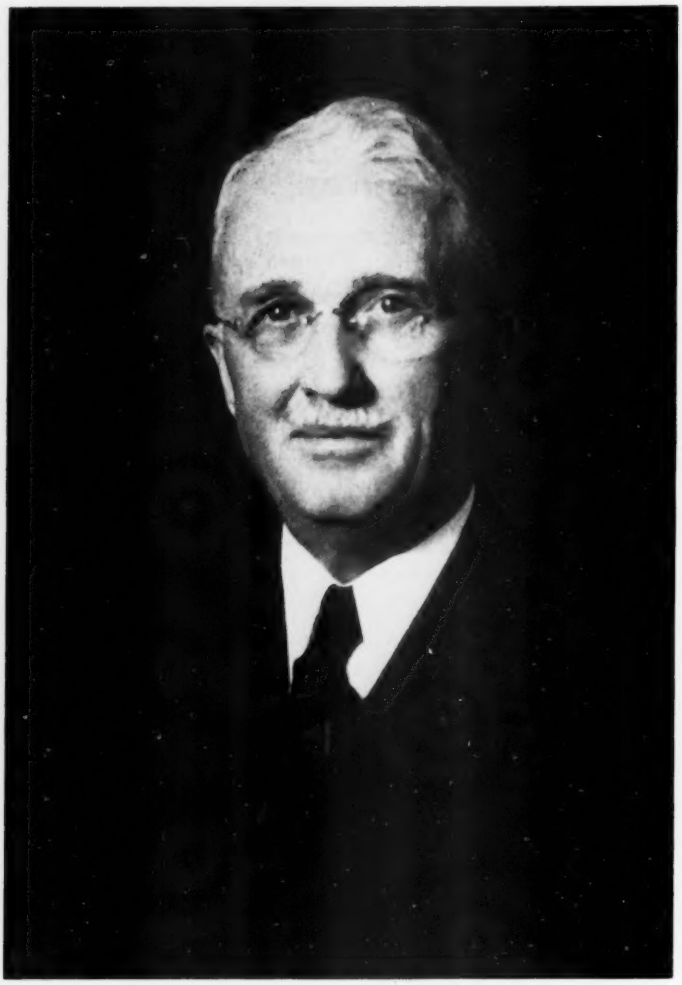
His society memberships included the Chicago and Illinois state medical societies, Chicago Society of Internal Medicine, Institute of Medicine of Chicago, American Heart Association, Central Society for Clinical Research, American Society for Clinical Investigation, American Association of Physicians, Central Interurban Club, and several others.

Dr. Gilbert is survived by his widow, the former Charlotte Louise Pettibone; a son, Dr. Robert P. Gilbert, also on the Northwestern University Medical School faculty; a daughter, Mary Elizabeth, and a sister, Julia E. Gilbert.

There was no time in his busy medical career in which Dr. Gilbert was not happily and industriously engaged in all aspects of the career of a well-rounded medical man—teaching, research, and active practice. His major research interest was heart disease, and he made noteworthy contributions on the inciting causes of coronary thrombosis, the action of digitalis, and bishydroxycoumarin treatment of myocardial infarction, etc.

As the senior member of the ARCHIVES board and close personal friend of Dr. Gilbert, Dr. Arthur Bloomfield has set down in the paragraphs which follow sentiments of the entire ARCHIVES board.

P. S. R.



NEWELL C. GILBERT, M.D.
1881-1953

The Editors of the ARCHIVES, and we are sure many of its readers, have heard with great distress of the death of Dr. Gilbert. For years Chief Editor of the ARCHIVES, he quietly bore the heavy burden of giving a final opinion on the papers submitted for publication, many of which required laborious revision. He always tried to preserve a logical balance between what was of genuine clinical interest and the more abstruse technical results of the laboratory, and his own soundness and long experience gave him an almost uncanny judgment in selecting the best material. How scrupulously fair he tried to be to the contributors is well known to the other editors, who can recall the long sessions when every acceptance or rejection was carefully reviewed.

A full appraisal of Dr. Gilbert's place in medicine and in his community cannot be given here. He was an outstanding clinician, not of the old school, but of the best school—that which rests on a basis of wide clinical experience and a careful general appraisal of the patient supplemented by judiciously indicated laboratory tests. He was no push-button doctor. But Dr. Gilbert did not stop with the practice of medicine alone. Problems suggested by the patient allowed him no rest until they were taken to the laboratory for an attempt at solution. Thus, his work on various aspects of disease, especially of the circulation, is widely known and has won for him the reputation of an outstanding investigator.

Dr. Gilbert's quiet and charming personality endeared him to all; yet his uncompromising adherence to what he felt were sound convictions both in medicine and in life in general could not be shaken. Along with others, those who had the good fortune to be his patients will be especially grieved at his loss.

ARTHUR L. BLOOMFIELD.

News and Comment

ANNOUNCEMENTS

Fellowships for Clinical and Experimental Research.—The establishment of two fellowships for clinical and experimental research has been announced by the Trustees of the Jewish Sanitarium and Hospital for Chronic Diseases. The Fellowships, named in the honor of the President of the Hospital, Mr. Isaac Albert, will be awarded during the fall of 1953.

Applicants should write to the Hospital Superintendent, Rutland Road and East 49th St., Brooklyn 3.

American Board of Nutrition Examinations.—The American Board of Nutrition will hold certifying examinations in Atlantic City, N. J., during April 1954. Completed applications of persons wishing to be considered for certification should be in the office of the Secretary not later than Feb. 1, 1954. Application forms may be obtained from the Secretary, Otto A. Bessey, Department of Biochemistry and Nutrition, The University of Texas School of Medicine, Galveston, Texas.

Assembly in Endocrinology and Metabolism.—The Endocrine Society and the University of Minnesota announce a postgraduate assembly in endocrinology and metabolism for physicians, the sixth annual assembly sponsored by The Endocrine Society, which will be presented on the University of Minnesota campus from Sept. 28 to Oct. 3, 1953. Lectures will be held in the Museum of Natural History Auditorium, while the facilities of the immediately adjacent Center for Continuation Study will be available for demonstrations and for the accommodation of registrants for the course.

All aspects of clinical endocrinology and metabolism will be taken up, and recent important advances in the field will be stressed. Informative demonstrations and illustrative clinical cases will be presented, and 10 panel discussions will provide registrants with opportunities to bring up special problems and questions. Each registrant will receive a booklet containing abstracts of all lectures.

The faculty for the assembly includes outstanding authorities in the field of endocrinology from various parts of the country as well as members of the faculty of the University of Minnesota Medical School and the Mayo Foundation. The program will be presented under the direction of Dr. Edward C. Reifenstein Jr., General Chairman for The Endocrine Society, and Dr. C. J. Watson, Professor and Head, Department of Medicine. Chairman of local arrangements on behalf of The Endocrine Society is Dr. Edmund B. Flink.

American Psychosomatic Society.—The American Psychosomatic Society will hold its 11th annual meeting at the Jung Hotel in New Orleans on Saturday and Sunday, March 27 and 28, 1954.

The Program Committee would like to receive titles and abstracts of papers for consideration for the program by Dec. 1, 1953. The time allotted for the reading of each paper will be 15 to 25 minutes. The committee is interested in investigations in the theory and practice of psychosomatic medicine as applied to adults and children in all the medical specialties and in contributions in psychophysiology and ecology.

The program committee requests that abstracts be submitted in quadruplicate to George L. Engle, M.D., Chairman, Program Committee, 551 Madison Ave., New York 22.

Eighteenth Annual Convention of the National Gastroenterological Association.—The National Gastroenterological Association will hold its Eighteenth Annual Convention and Scientific Sessions at The Biltmore Hotel in Los Angeles on Oct. 12, 13, and 14, 1953.

The program will include a symposium on cirrhosis of the liver and panel discussions on "Peptic Ulcer," "Diseases of the Large Bowel," and "Latest Developments in Cancer Research."

There will be additional papers on interesting subjects in gastroenterology and related fields.

After the Convention, on Oct. 15, 16, and 17, 1953, the Association's fifth annual course in postgraduate gastroenterology will be given at The Biltmore Hotel and the College of Medical Evangelists, in Los Angeles. The course will be under the personal direction of Drs. Owen H. Wangensteen, of Minneapolis, Minn., and I. Snapper, of Chicago, Ill., who will be assisted by a faculty from the medical schools in and around Los Angeles.

The Scientific Sessions on October 12, 13, and 14 are open to all physicians without charge. The postgraduate course will only be open to those who have matriculated in advance.

Further information concerning the program and details of the postgraduate course may be obtained by writing to the Executive Officer, National Gasthroenterological Association, 1819 Broadway, New York 23.

American Heart Association Fellowships and Research Grants-In-Aid.—Applications for Established Investigators and for Research Fellows for the fiscal year 1954-1955 must be received in the office of the Association not later than Sept. 15, 1953.

Applications for Research Grants-In-Aid for 1954-1955 must be received not later than Dec. 1, 1953.

Information booklets and application blanks may be obtained from the Medical Director.

Annual Meeting of the American Heart Association, 1954.—The annual meeting of the American Heart Association in 1954 will be held at the Conrad Hilton Hotel in Chicago. The assembly panels and the general assembly will be held on Thursday and Friday, April 1 and 2, and will be followed by a specific scientific program on clinical cardiology on Saturday and Sunday, April 3 and 4, conducted under the auspices of the newly formed section on clinical cardiology of the scientific council. These sessions will immediately precede the annual meeting of the American College of Physicians.

Scientific Program of the Section on Clinical Cardiology, 1954.—The section on clinical cardiology of the American Heart Association will sponsor a two-day scientific program at the Conrad Hilton Hotel in Chicago on April 3 and 4, 1954. This program will constitute a portion of the annual meeting of the American Heart Association and immediately precedes the annual session of the American College of Physicians. The meeting will be open to all members of the medical profession. Dr. Wright R. Adams, of Chicago, is chairman of the program committee. Members of the American Heart Association who wish to present papers should send a 250 to 300 word abstract of the proposed paper to Dr. Charles D. Marple, Medical Director, American Heart Association, Inc., 44 East 23rd Street, New York 10. All papers should be on subjects of distinct clinical interest. The deadline for the receipt of abstracts is Jan. 1, 1954.

Annual Scientific Sessions, 1954, and the Second International Congress of Cardiology.—The 27th scientific sessions of the American Heart Association will *not* be held at the usual time in 1954, but will take place following the Second International Congress of Cardiology, in September. The International Congress of Cardiology will be held in Washington, D. C., Sept. 12 through 15, 1954, and the scientific sessions of the American Heart Association will also be held in Washington, Sept. 16 through 19.

Van Meter Prize Award.—The American Goiter Association again offers the Van Meter Prize Award of $300.00 and two honorable mentions for the best essays submitted concerning original work on problems related to the thyroid gland. The award will be made at the annual meeting of the Association, which will be held in Boston, April 29 and 30 and May 1, 1954, providing essays of sufficient merit are presented in competition.

The competing essays may cover either clinical or research investigations; should not exceed 3,000 words in length, and must be presented in English, and a typewritten double-spaced copy in duplicate should be sent to the Corresponding Secretary, Dr. John C. McClintock, 149½ Washington Ave., Albany 10, N. Y., not later than Jan. 15, 1954. The committee which will review the manuscripts is composed of men well qualified to judge the merits of the competing essays.

A place will be reserved on the program of the annual meeting for the presentation of the prize award essay by the author, if it is possible for him to attend. The essay will be published in the annual proceedings of the Association.

Thirty-Sixth Annual Conference of the American Occupational Therapy Association.—The American Occupational Therapy Association will hold its 36th annual conference, Nov. 13 to 20, at the Shamrock Hotel, Houston, Texas. There will be a preconference institute with the theme "Research in Occupational Therapy" held from Nov. 17 to 20. The general program will be given from Nov. 17 to 20 with the theme "Refining our Resources."

The papers to be read include "Present Treatment in Tuberculosis," by Dr. William S. Schwartz, Chief, Professional Services, Veterans Administration Hospital, Octeen, N. C.; "Current Trends in the Treatment of Burns," by a representative from the surgical research unit, Brooke Army Hospital; "Training in the Use of Upper Extremity Prostheses," by Capt. Mary Berteling, Brooke Army Hospital, and "Occupational Therapy for the Aged—Minnesota's Program," by Miss Genevieve Cummings, Department of Public Welfare, St. Paul.

Further information may be obtained from Miss Lucile L. Lacy, O.T.R., Veterans Administration Hospital, Houston, Texas.

Thirty-Ninth Annual Clinical Congress of the American College of Surgeons.—The thirty-ninth annual clinical congress of the American College of Surgeons is to be held in Chicago, Oct. 4 through 9, 1953.

Surgical techniques and new developments in surgery will be covered in this five-day meeting. The program will include formal scientific papers, panel discussions, symposia, postgraduate courses, surgical forums, medical motion pictures, ciné clinics, color television, and exhibits.

Headquarters will be the Conrad Hilton Hotel. Dr. Thomas C. Douglass, Associate Professor of Surgery, Northwestern University, and Attending Surgeon, Passavant Memorial Hospital, is chairman of the Chicago committee on arrangements.

GENERAL NEWS

Books for Israel.—A communication has been received from representatives of "Books for Israel," 115 King St., New York 1, pointing out the great need in that country for medical texts published since 1940.

Books on clinical medicine and the related sciences, such as biochemistry, bacteriology, physiology, etc. will be gratefully received by the "Books for Israel" distributing committee.

Up to 70 lb. may be sent by parcel post, at 8¢ for the first pound and 4¢ each additional pound, marked "Book Rate." Please give return address of individual or organization, so that your gift may be acknowledged. Funds for shipment from New York to Israel have been provided under Point 4, United States State Department, sponsors of this project.

Books

Pathology of the Heart. Edited by S. E. Gould, M.D., D.Sc.; collaborators are A. H. Baggenstoss, Alexander Barry, J. E. Edwards, S. E. Gould, H. D. Green, W. T. Hill, E. B. Krumbhaar, A. R. Moritz, G. B. Myers, B. M. Patten, Otto Saphir, W. A. Stryker, and W. B. Wartman, with a foreword by H. T. Karsner. Price, $25.50. Pp. 1,040, with 690 illustrations and 6 plates in full color. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1953.

Although heart disease has been in the center of interest of physiologists, pathologists, and clinicians for a long time and our knowledge in this field has advanced enormously in the last three decades, the treatment of heart disease has made only slow steps forward since the introduction of digitalis by Withering. In recent years the development of operative intervention in congenital anomalies and in acquired valvular lesions of the heart has awakened new interest and has brought new hope to the physician and his cardiac patients. Cardiology has been established as a separate specialty in its own right. The time will soon come when all the larger hospitals in this country will have their cardiology departments, with modern diagnostic and surgical facilities, staffed by experienced specialists.

This is the first modern book for students of cardiology which covers the anatomical, physiological, morphological, and functional pathological aspects of this field in one volume, emphasizing clinicopathological correlations. Edited and written by acknowledged experts in their fields, this monograph attempts to fulfill the need of an adequate clinical pathology of the heart useful to both clinicians and pathologists.

Following a brief review of the history of cardiac pathology, the development of the heart is treated in 66 pages. The understanding of this difficult subject is supported by visualization of the material in abundant and good diagrams. The next chapter presents the normal anatomy and histology. The following two chapters are devoted to the normal physiology of the heart and abnormal cardiac functions. Recent data on cardiac catheterization, which has changed in many ways our former concepts of normal and abnormal cardiac dynamics, are thoroughly considered. The bibliography is extensive and up to date, although some of the recent foreign work is ignored.

Next comes a description of congenital malformations, covering almost 240 pages. The outstanding value of this portion lies in the discussion of recently established dynamic changes following surgical repair of some of these anomalies. A good bibliography is at the end of each chapter.

Degenerative diseases, vascular lesions, and rheumatic and nonrheumatic inflammatory diseases of the heart are covered in the following chapters. The descriptive pathology is always accompanied by functional pathological correlations. Parasitic diseases, injuries, and neoplasms of the heart are treated in three separate chapters. In the last chapter clinicopathological correlations are summarized, giving a final emphasis to the clinical aspects of this subject, since "the lessons of pathology must be brought into relation with the living patient." An appendix is devoted to pathological techniques for the examination of the heart.

The editor and his collaborators have to be congratulated for this excellent book. Their objective of presenting accurate and authentic data has in every way been fulfilled. This volume will be of great value as a reference book for those who have devoted themselves to diagnostic and surgical cardiology or who want to do special pathological studies in this field. Also, internists interested in cardiology will find it very instructive. However, for general practitioners and probably for medical students the book is too extensive and specific.

The publishing is outstanding, representing a superb example of the lithography in this country. It is unfortunate that its excessive price will restrict ownership of the book to a very small group.

Carbohydrate Metabolism: Correlation of Physiological, Biochemical and Clinical Aspects. By Samuel Soskin, M.D. and Rachmiel Levine, M.D. Second Edition. Price, $8.50. Pp. 346, with charts and tables. University of Chicago Press, 58th and Ellis Ave., Chicago 37, 1952.

The second edition of this book, like the first, covers various aspects of carbohydrate metabolism, and the presentation of this material in one volume is certainly of great value to the student. The authors have succeeded in their effort to produce a book which will aid the student in obtaining a unified concept of the various aspects of carbohydrate metabolism.

The sections dealing with enzymes and hormonal regulation of metabolism have been enlarged. Data and information obtained from recent isotopic studies have been added, and the implication of their results on intermediate metabolism is discussed. In the reviewer's opinion, the authors have again given too much emphasis to the question of the relative importance of the overproduction theory as compared to the underutilization theory in the diabetic state.

The volume continues to be an excellent source of information and is a useful book for anyone seriously interested in carbohydrate metabolism as well as for students of physiology, biochemistry, and medicine.

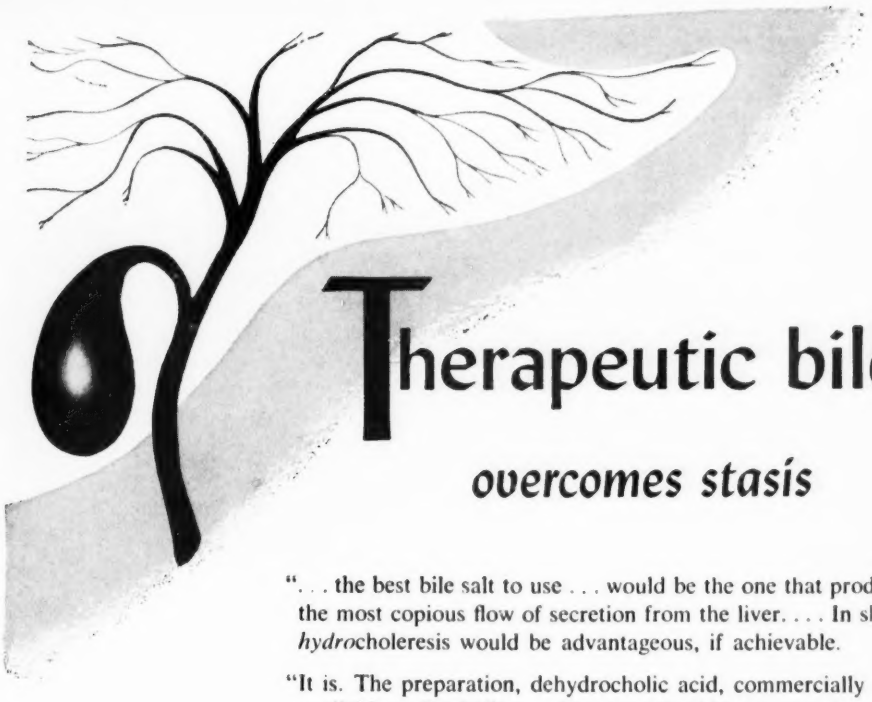
Diagnostic Tests in Neurology: A Selection for Office Use. By Robert Wartenburg, M.D., with Foreword by Sir Gordon Holmes and Stanley Truman, M.D. Price, $4.50. Pp. 228, with 62 illustrations. Year Book Publishers, Inc., 200 E. Illinois St., Chicago 11, 1953.

This book is highly recommended to all internists and general practitioners. It is not a textbook of neurology. It is not even a textbook of physical diagnosis in neurology. It is, instead, a book packed with an impressive selection of those tests which the author considers to be of greatest value in diagnosing neurological conditions. It is, in the vernacular of the medical student, a "book of pearls."

The whole emphasis of the book is on clinical versus laboratory diagnosis, and the introduction is devoted primarily to a discussion of the various aspects of this question. No tirade against laboratory tests, it does, nevertheless, request a reevaluation of the criteria all too generally accepted as indications for these tests. As the author states, laboratory procedures are never a substitute for clinical observation and often seem necessary only because the clinical examination has not been adequate.

The book is divided into seven sections—two on nerves, cranial and peripheral, and five on systems, the pyramidal, extrapyramidal, sensory, cerebellar, and vasomotor trophic. Approximately 100 tests and reflexes are described. The author includes a few of the old standbys, simplifying some, adding to others. He explains why the Hoffman reflex is not pathological as such, as it is so often thought to be. He discusses the physiology and evaluation of the Babinski reflex. He includes three easy methods of eliciting the triceps surae, or Achilles, reflex and a simple method of local reinforcement. The superficial and deep abdominal reflexes are described, as well as the significance of dissociation between them.

However, most of the tests and reflexes included are those not found in the usual neurological text. They are tests that should be added to the practitioner's basic repertoire to help in the further evaluation of nervous system disorders; to help bring out a latent or mild spastic paralysis or facial paresis, and to help differentiate between hysterical and organic conditions, between polyneuritis and tabes, and between the various conditions causing dissociated anesthesia. Lid vibration and Achilles tendon palpation are offered as the tests which will often be the only sign of a spastic paralysis or peripheral nerve disturbance, respectively, and supraclavicular pressure as a test for the scalenus anticus syndrome. The author describes the counter pressure phenomenon seen in dystonia, jugular compression, and neck bending tests for localization of intradural lesions and the knee dropping test for pyramidal lesions, a test "perhaps more sensitive than the Babinski." These, and the numerous other inclusions, make this book an unusually valuable addition to the library of any physician in contact with neurological patients.



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*Beckman, H.: Pharmacology in Clinical Practice, Philadelphia, W. B. Saunders Company, 1952, p. 361.

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1. J. A. M. A. 151 (1953):5, p. 366

2. Postgraduate Med. J. 10(1951), p. 317

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BIBLIOGRAPHY: *1. Humphreys, P., et al.: Angiology* 3:1 *(Feb.) 1952. 2. Plotz, M.: New York State J. Med.* 52:2012 *(Aug. 15) 1952. 3. Dailheu-Geoffroy, P.: L'Ouest-Medical, vol. 3 (July) 1950.*

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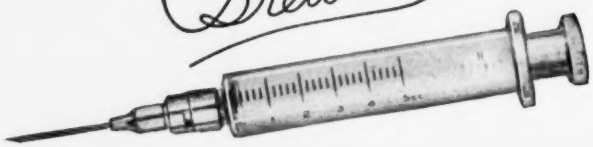

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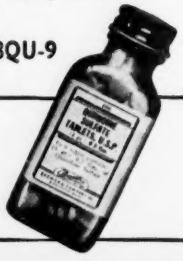

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1. Skehadi, W. H.: *Am. Jour. Roentgenol.*, 68:360, Sept., 1952.

2. Everett, E. P., and Bigler, L. G.: *Radiology*, 58:524, Apr. 1952.

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